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The Synthesis, Characterization
and Attempted Polycondensation of
2,3,6-Tri-O-Benzoyl-*a*-D-Glucopyranosyl Bromide

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June, 1961

THE SYNTHESIS, CHARACTERIZATION AND ATTEMPTED POLYCONDENSATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

A thesis submitted by

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INTRODUCTION

In the field of wood chemistry, identification of the sugar units and linkages present in oligo- and polysaccharidic materials isolated from wood has been an important task, since the linkages and sugar units present in the carbohydrate fraction of wood greatly affect the physical properties of the pulps and papers made from the wood. Such methods as methanolysis, hydrolysis, methanolysis followed by partial hydrolysis, and oxidation have been found useful in designating what sugar units and linkages are present; however, these methods are incomplete because they do not determine in what basic order the linkages and sugar units exist. These methods all have in common the practice of breaking down the original material isolated from wood into its basic components or derivatives of its basic components. Ultraviolet and infrared spectroscopy have also been found useful in indicating what sugar units make up a given unknown carbohydrate fraction of wood.

From the standpoint of synthesizing material from basic constituents, two types of chemical techniques have been employed in the past. First, there are the works of Mora, Pacsu, Bishop and Ricketts (1-8) in which a sugar solution was evaporated to a sirup in the presence of an inorganic acid, resulting in a polymer containing the sugar as a repeating unit. This technique, however, is lacking in that no control can be exercised over the type of linkages obtained. In the second type of synthesis, oligosaccharides were produced by adding, in a series of condensation reactions, one sugar unit to the reaction product from the

previous reaction. This technique is very laborious and the yields are very low.

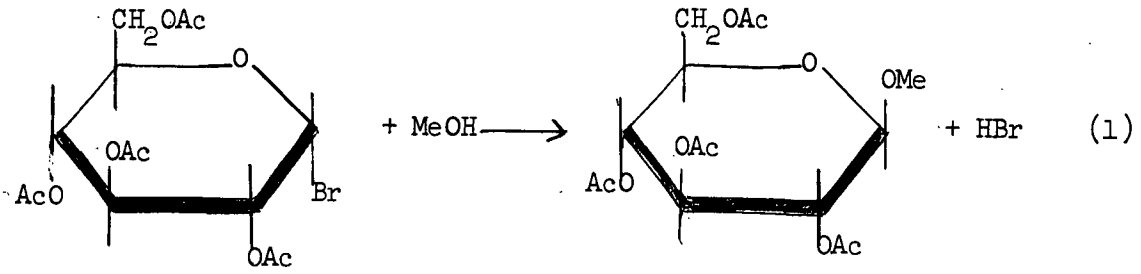
Enzymatic methods have probably resulted in the most successful attempts to synthesize oligo- and polysaccharides. When Acetobacter acetigenum or Acetobacter xylinum was used as an enzyme system, it was possible to produce a compound identical to cellulose in most properties, differing only in nitrogen content (9-14). It is theorized that this higher nitrogen content is a result of inclusion of some of the original cell body in the polysaccharide.

The purpose of this thesis was to investigate a new technique which might be used to synthesize chemically oligosaccharides in a single reaction with exactly known linkages and with sugar units similar to those isolated from wood. Since this technique involved the synthesis of a new, partially acylated glucosyl halide, it was also desirable to investigate the reactivity of this new compound with respect to fully acylated glucosyl halides by solvolysis reactions.

The limitation of synthesizing an oligosaccharide with exactly known linkages and sugar units required that a material be available which, under a given set of conditions, would condense in a polymer homologous series of specific oligosaccharides. A preliminary requirement, therefore, was to employ a reaction which would yield only given linkages yet would be applicable to polycondensation. The Koenigs-Knorr reaction appeared to fulfill this stipulation, with a bifunctional glucose molecule.

THE KOENIGS-KNORR REACTION

In 1900 Koenigs and Knorr (15) discovered that a fully acetylated glycosyl halide would react with methanol to form the methyl β-D-glycoside as shown in Equation (1).



(1)

The yield they obtained was very low, and since that time a number of improvements have been made which increase the usefulness of this reaction.

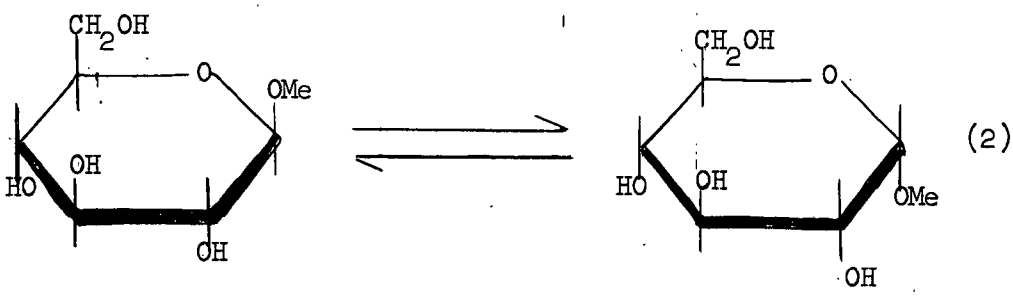
ACID ACCEPTORS

The addition of an acid acceptor or a condensing agent has been shown to greatly increase the yields from a Koenigs-Knorr reaction. It is hypothesized that the acid acceptor serves two purposes: First, it acts as a pseudo catalyst by increasing the rate of dissociation of the C-1 halogen bond; second, it ties up the liberated hydrogen bromide which tends to cause transglycosidation and transesterification.

Several salts have been used as acid acceptors, the most frequently used being silver oxide and silver carbonate. Mercuric salts have also been used; however, the silver salts always lead to complete inversion

of configuration, whereas the mercuric salts can lead to a mixture of both alpha and beta anomers.

There are two types of transglycosidation which may be caused by the liberated hydrogen bromide. The following is an example of the first type: When a methyl β-D-glycoside is treated with hydrogen chloride in methanol, it is partially transformed to the alpha anomer, thus giving a mixture of alpha and beta anomers as shown in Equation (2).



(2)

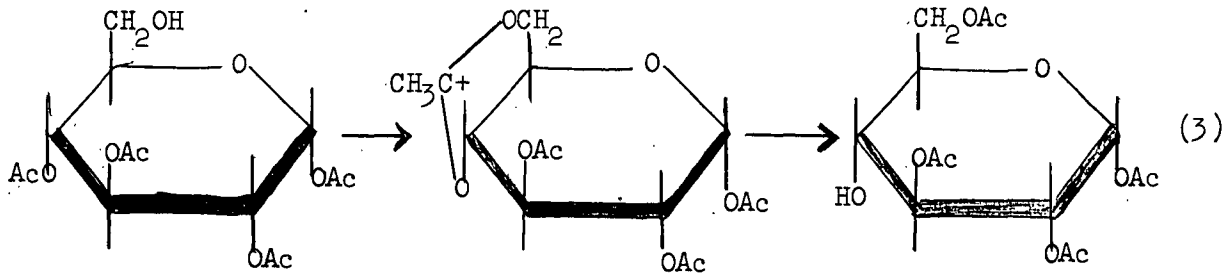
Methyl β-D-glucopyranoside Methyl-α-D-glucopyranoside

The second type of transglycosidation occurs when an oligosaccharide is treated with hydrogen chloride to yield a new linkage. For example, when cellulose is hydrolyzed with hydrogen chloride, some of the cellulose is rearranged to the β1→6 linked gentiodextrins. This factor would be pertinent in any Koenigs-Knorr reaction which led to the synthesis of oligosaccharides.

Transesterification is the phenomenon which occurs when an acyl group on a partially acylated glucose molecule* moves from one hydroxyl group to an adjacent free hydroxyl group. This phenomenon, also called acyl migration, is most common when acetyl esters are used and is catalyzed by either acidic or basic reagents. Lemieux (16-18) has studied

* All references to glucose or glucosyl refer to the pyranose form.

this phenomenon extensively and postulates that the mechanism goes through an orthoester intermediate as shown in Equation (3).



(3)

The usual direction of migration is away from the lactol carbon.

DESICCANTS

It has been advantageous to incorporate internal desiccants in the reaction which will combine with free water as quickly as it is formed. The incorporation of acid acceptors such as silver oxide or silver carbonate in the Koenigs-Knorr reaction leads to the production of free water as shown in the following equation:

$$4HOG\ell Br + Ag_2CO_3 \longrightarrow 2HOG\ell OG\ell Br + 2\ AgBr + H_2O + CO_2 \qquad (4)$$

The one mole of water can produce two moles of the free sugar as shown by Equation (5).

$$2HOG\ell Br + Ag_2CO_3 + H_2O \longrightarrow 2HOG\ell OH + 2AgBr + CO_2 \qquad (5)$$

It is obvious that the production of the free sugar reduces the efficiency of the Koenigs-Knorr reaction. Evans and Reynolds (19) found that incorporating Drierite, anhydrous calcium sulfate, into a reaction which produced gentiobiose by means of the Koenigs-Knorr reaction increased the yield from 25 to 80%.

CATALYSTS

A catalyst, such as iodine, was found useful in accelerating the rate of reaction, since the incorporation of Drierite slowed down the rate of reaction for some anomalous reason. Probably the iodine functions by exchanging with the bromine atom on the glycosyl bromide, thus making a more reactive halide.

APPLICATION OF THE KOENIGS-KNORR REACTION TO DISACCHARIDE SYNTHESIS

Many investigators have utilized the Koenigs-Knorr reaction to synthesize simple glycosidic linkages with alcohols and phenols. Table I illustrates some of the various glycosidic linkages which have been synthesized.

TABLE I

SIMPLE GLYCOSIDES PRODUCED BY THE KOENIGS-KNORR REACTION (20-23)

O-Acyl-glycosyl halides	Aglycons
Tetra-O-acetyl-α-D-glucosyl bromide	Phenol
Tetra-O-acetyl-α-D-glucosyl chloride	Methanol
Tri-O-acetyl-α-D-xylosyl bromide	Adenosine
Tetra-O-acetyl-α-D-galactosyl bromide	o-Nitrophenol
Tetra-O-acetyl-α-D-mannosyl bromide	α-Hydroxypropiovanillone
	α-Hydroxypropiosyringone
	Acetovanillone
	α-Acetoxypropiovanillone
	α-Acetoxypropiosyringone

It has been found possible to produce a disaccharide by condensing a partially acylated glucose molecule containing only one free hydroxyl group with a fully-acetylated glycosyl halide. Five such condensations are illustrated in Fig. 1 exemplifying five different glucose-glucose linkages.

It should be noted that in the condensation of a glycosyl halide with an alcohol or phenol it is possible to have the hydroxyl group in large excess (the alcohol sometimes being the solvent) and high yields are usually obtained; whereas, when a sugar containing one free hydroxyl group is used, the reaction is conducted in inert solvents and solubility limits the amounts of excess hydroxyl which can be added. Therefore, the yields are usually lower.

It is thus seen that the Koenigs-Knorr reaction is a useful condensation reaction for synthesizing a given glycosidic linkage.

APPLICATION OF THE KOENIGS-KNORR REACTION TO POLYCONDENSATION

The use of the Koenigs-Knorr reaction in the synthesis of a series of oligosaccharides falls under the general classification of condensation polymerization. Polycondensation involves substances possessing two or more functional groups which undergo straightforward chemical reaction with one another.

Haq and Whelan (24) noted that 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide (I) prepared by Zemplen and Gerecs (25) was a bifunctional molecule containing a reactive bromide atom at the lactol carbon and a reactive hydroxyl group on C-6.

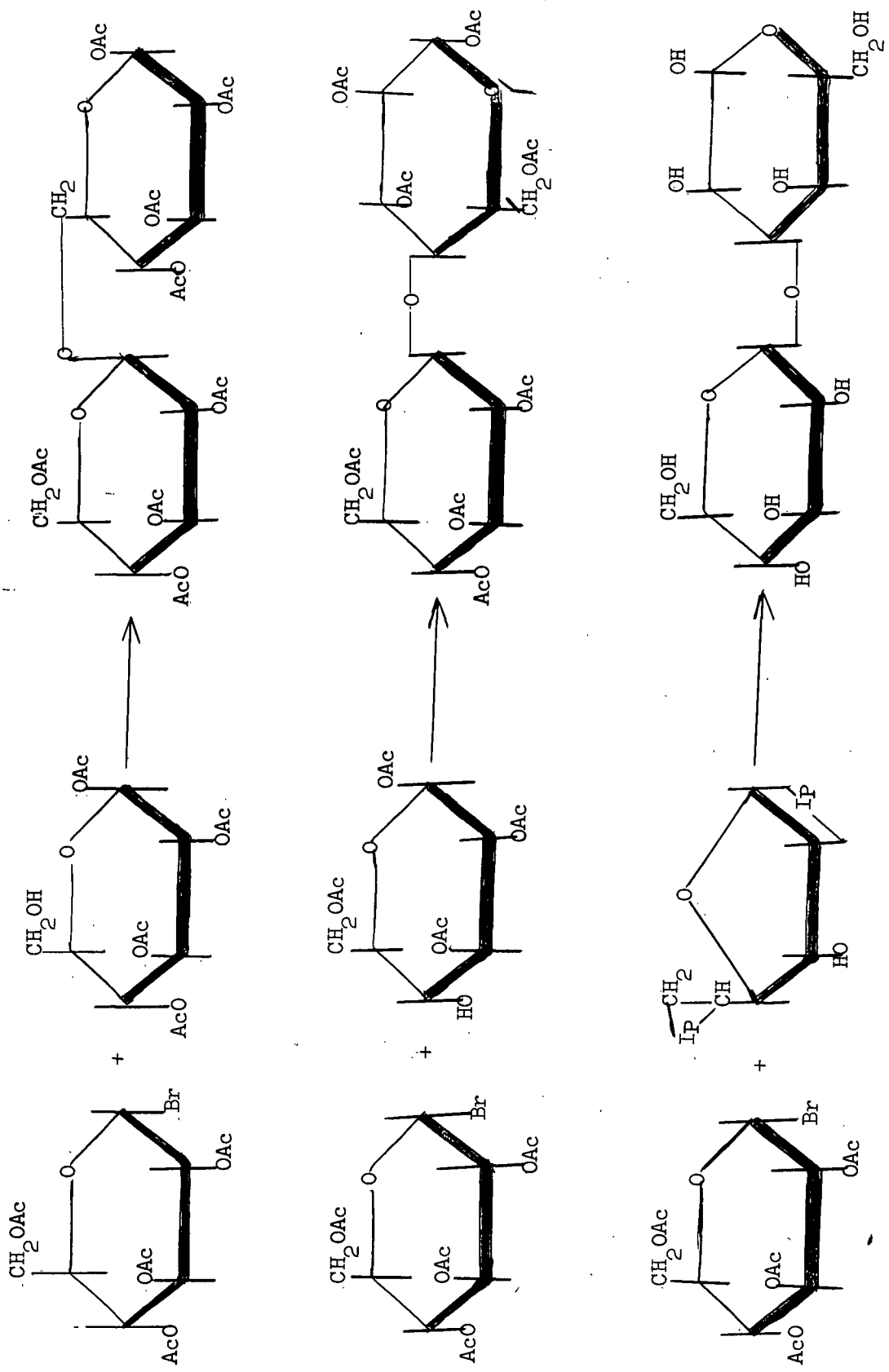


Figure 1. The Synthesis of Disaccharides
By Means of the Koenigs-Knorr Reaction

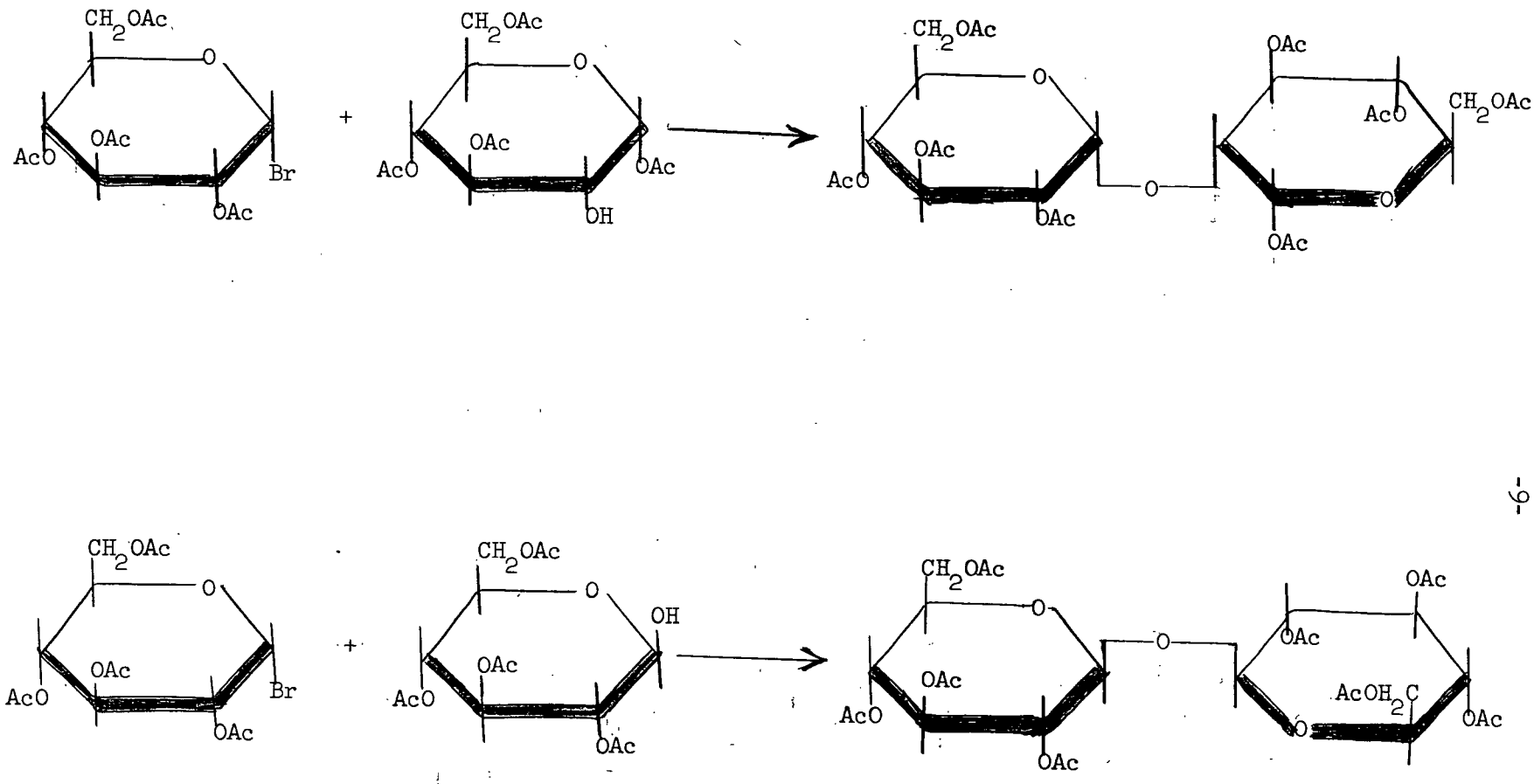
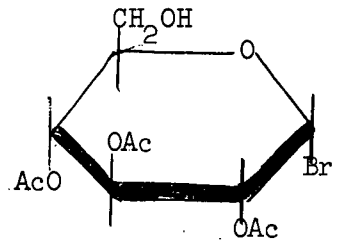


Figure 1 (Cont'd). The Synthesis of Disaccharides
By Means of the Koenigs-Knorr Reaction



2,3,4-tri-O-Acetyl-α-D-glucopyranosyl bromide (I)

Haq and Whelan reasoned that they should be able to form oligosaccharides by condensing the hydroxyl group of one sugar molecule with the halogen of another sugar molecule to form the β 1→6 linked gentiodextrin series of oligosaccharides as shown in Equation (6),

$$n\ HOGlBr + HOGlBr \xrightarrow[2\text{-}4^{\circ}C.]{Ag_2O} HO(GlO)_nGlBr + n\ HBr \qquad (6)$$

where Gl represents the appropriate sugar nucleus.

Haq and Whelan (24) had conducted a preliminary small-scale experiment (5 g. of 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide) to determine the length of time required for the experiment to reach completion. Their small-scale experiment indicated that nine days were sufficient to attain completion. A larger scale experiment was conducted, therefore, using 35 g. of 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide, 18 g. of freshly prepared silver oxide, 50 g. of Drierite, and 1 g. of iodine. The reaction products were separated by gradient elution column chromatography.

REACTION PRODUCTS AND YIELDS

The products from this reaction proved to be mainly oligosaccharides of the gentiodextrin series, thus confirming Haq and Whelan's original

premise. Also obtained were levoglucosan and glucose, combined with lesser amounts of by-product oligosaccharides. Table II indicates the yields from the large-scale experiment of Haq and Whelan (24).

TABLE II

YIELDS OF FREE GENTIODEXTRINS AND BY-PRODUCTS

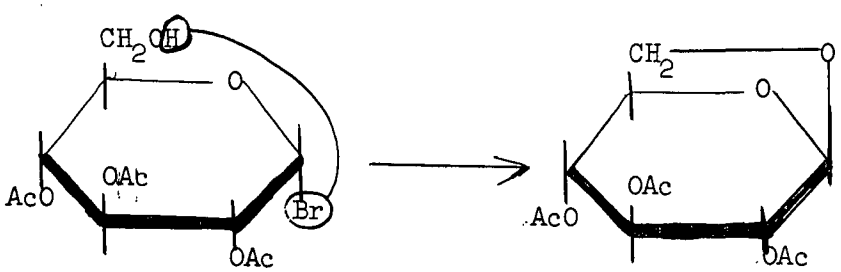
(35 g. 2,3,4-tri-O-Acetyl-α-D-glucopyranosyl bromide)

Sugar	Yield, g.
Glucose	1.41
Levoglucosan	1.64
Gentiobiose	2.10
Gentiotriose	3.30
Gentiotetraose	0.74
Gentiopentaose	0.34
Gentiohexaose	0.18

A weight fraction distribution curve is shown in Fig. 2. The presence of heptaose, octaose, and nonaose was indicated from paper partition chromatography, ionophoresis, and molecular rotation data.

Three main by-products were obtained from the large-scale reaction: Levoglucosan, cellobiose and beta, beta-trehalose. The combined amounts of cellobiose and beta, beta-trehalose only amounted to 13 mg.

Levoglucosan was formed by intramolecular condensation between the two functional groups on the 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide. See Equation (7).



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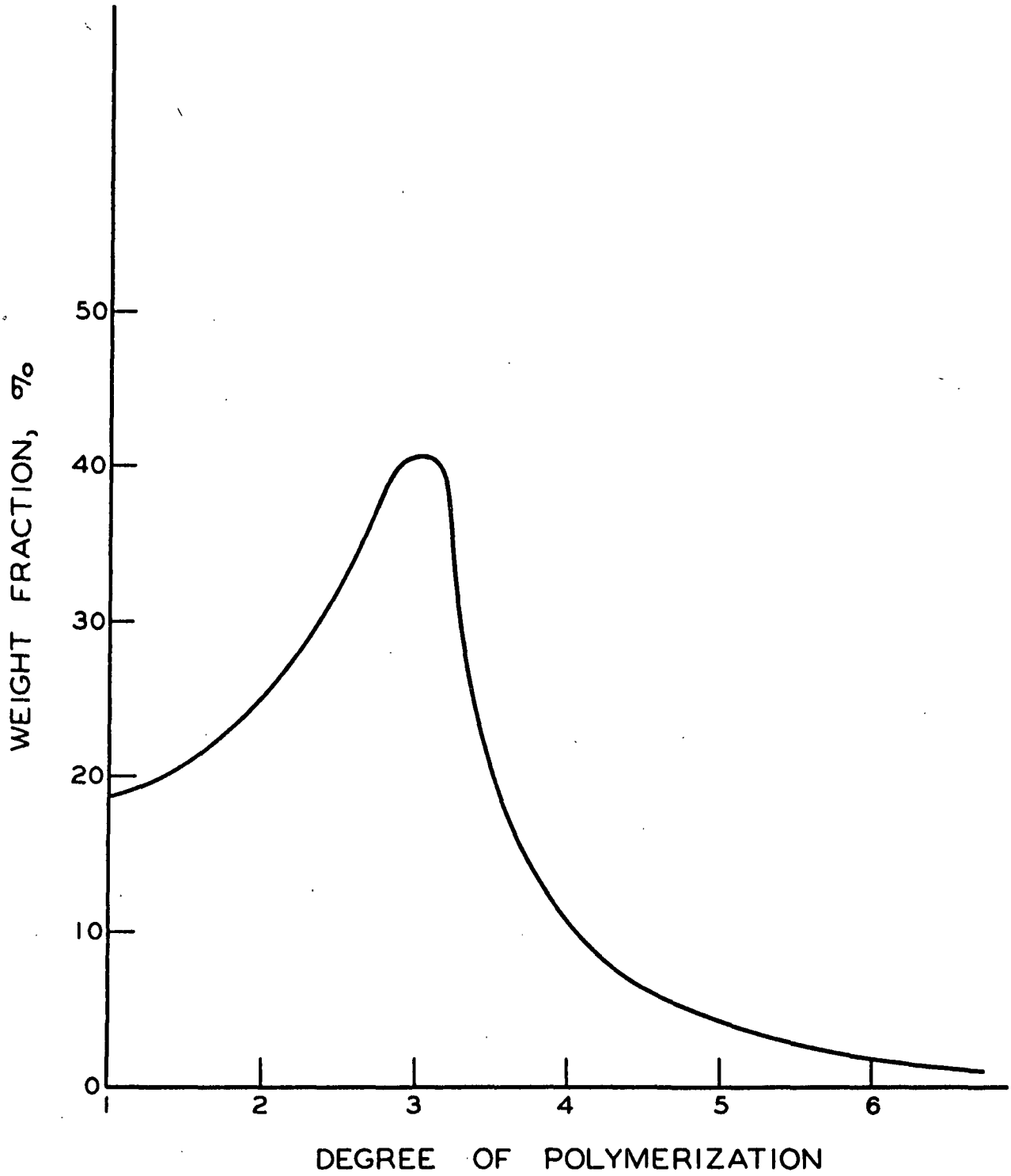
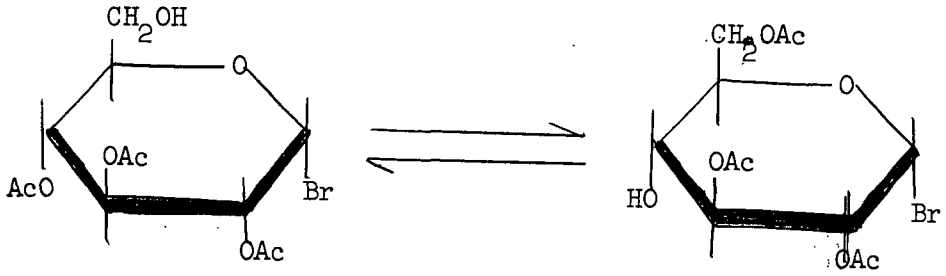


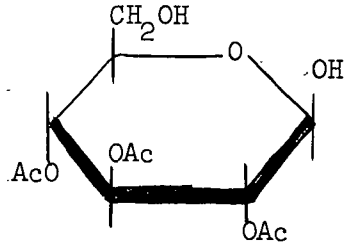
Figure 2. Distribution Curve for the Synthesis of β 1→ 6 Linked Oligosaccharides

Cellobiose was probably formed by acyl migration of some of the acetyl groups from C-4 to C-6 and subsequent condensation with the original monomer. Thus, instead of 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide, the monomer would be 2,3,6-tri-O-acetyl-α-D-glucopyranosyl bromide. See Equation (8).



(8)

Beta, beta-trehalose was formed when some of the water of reaction formed 2,3,4-tri-O-acetyl-β-D-glucopyranose (II) and this compound condensed with the original monomer.



2,3,4-tri-O-Acetyl-β-D-glucopyranose (II)

STATEMENT OF THE PROBLEM

Since the Koenigs-Knorr reaction was successful as a polycondensation reaction in synthesizing the gentiodextrin series of oligosaccharides, it appeared desirable to investigate this technique for its applicability to the synthesis of oligosaccharides containing other than the 1→6 repeating linkage. In particular, the synthesis of the cellodextrin series of oligosaccharides was considered as a logical step in the utilization of this reaction since the 1→4 linkage is most prevalent in nature.

The initial purpose of this thesis, therefore, was to investigate the applicability of the Koenigs-Knorr reaction to the synthesis of the cellodextrin series of oligosaccharides through a single polycondensation reaction.

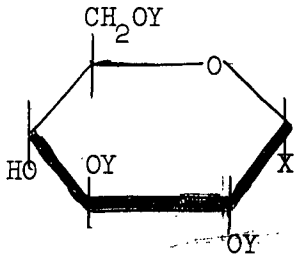
This investigation was divided into two parts:

1. the synthesis and characterization of a suitable material which theoretically should condense to yield the cellodextrins, and
2. the attempted condensation of this material to yield the cellodextrins.

Since it was found that this polycondensation was not as successful as Haq and Whelan's it also became a purpose to attempt to demonstrate a reason for the differences in the results of the polycondensations.

EXPERIMENTAL DATA

The primary requirement for success of this thesis was the preparation of a suitable compound with a reactive group on C-1, an unsubstituted C-4 hydroxyl group, and all the other hydroxyl groups rendered inert by reacting them with blocking groups. This compound would be a 2,3,6-trisubstituted-α-D-glucopyranosyl halide (III), which theoretically should condense under conditions of the Koenigs-Knorr reaction to yield the cellodextrins.



2,3,6-Trisubstituted-α-D-glucopyranosyl halide (III)

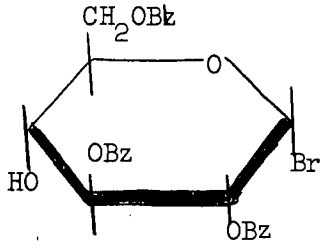
SELECTION OF THE HALIDE ATOM

Bromine was selected as the halide atom since it is a suitable balance between reactivity and stability. The stabilities of the acyl glycosyl halides are in the order fluoride > chloride > bromide > iodide. The fluorides are extremely stable and may even be deacetylated without loss of fluorine to give the corresponding glycosyl fluorides. The iodides, on the other hand, are unstable compounds which, even in favorable cases, decompose at room temperature within two weeks (20).

SELECTION OF THE BLOCKING GROUP

The blocking groups must fulfill two requirements to be useful. First, they must render the 2,3 and 6 carbons inert; and second, they must be removed from the condensation products by a reaction which will not attack the glycosidic linkages. Benzoate esters were selected as inert blocking groups because they are much less susceptible to acyl migration than acetate esters; nevertheless, they can be removed from the oligosaccharides by saponification to give the free cellodextrins. Only one instance of acyl migration with benzoate esters could be found in the literature (47). Methyl, tosyl or mesyl blocking groups could also have been selected; however, these groups are not easily removed without destroying the identity of the condensation products.

The selection of benzoate esters as blocking groups and bromide as the halide atom, therefore, identifies the desired monomer as 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide (IV).



2,3,6-tri-O-Benzoyl-α-D-glucopyranosyl bromide (IV)

SYNTHESIS OF A 1-4 BIFUNCTIONAL GLUCOSE MOLECULE

The 1,2,3,6-tetra-O-benzoyl-D-glucose, first prepared by Brigl and Grüner (26) according to the scheme shown in Fig. 3, was a good starting point for the synthesis of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide requiring only the substitution of a bromide group for the benzoxy ester on C-1. Titanium tetrabromide was used as a brominating agent, although it had never previously been used to replace benzoate esters in the halogenation of a partially esterified glucose molecule. The usual method of halogenating esterified sugars with hydrobromic acid in acetic acid was not applicable because the acetic acid would esterify the free C-4 hydroxyl group.

It was possible to obtain white, needlelike crystals melting at 161-163°C. with decomposition at 163°C. and a specific optical rotation of +181.3° (c = 1, chloroform) which were thought to be 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide. The details for this preparation can be found in the experimental procedure section (p. 71).

IDENTIFICATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

CARBON, HYDROGEN, BROMINE DETERMINATION

A sample of the unknown crystalline material obtained by halogenating 1,2,3,6-tetra-O-benzoyl-D-glucose with titanium tetrabromide was sent to Huffman Analytical Laboratories* for determination of carbon, hydrogen,

* Huffman Microanalytical Laboratories, P. O. Box 125, Wheatridge, Colorado.

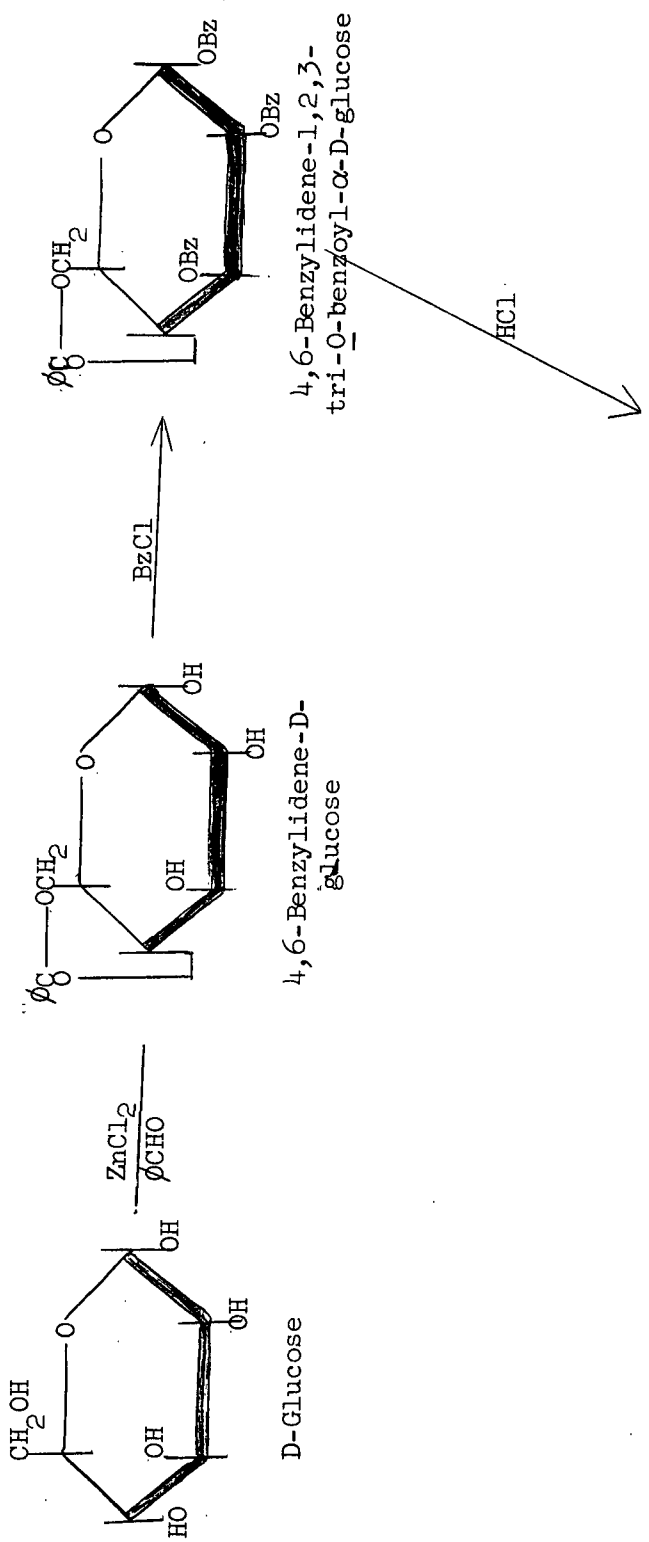


Figure 3. Synthesis of 1,2,3,6-tetra-O-Benzoyl-D-glucose

and bromide. The results are as follows, calculated for $C_{27}H_{23}O_8Br$: C, 58.40; H, 4.64; Br, 14.37; O, 23.09. Found: C, 58.60; H, 4.52; Br, 14.24; O (by difference), 22.84. These data are in accordance with a glucose molecule substituted with three benzoate esters and a bromide group.

PREPARATION OF A DERIVATIVE

Methyl 2,3,6-tri-O-benzoyl-β-D-glucopyranoside was prepared by reacting 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide in methanolic chloroform for 24 hours in the presence of freshly prepared silver oxide. This reaction resulted in a compound having a melting point of 144-145°C. (uncorr.) and a specific optical rotation of +81.6° (c = 2, chloroform). These data compare favorably with the properties of methyl 2,3,6-tri-O-benzoyl-β-D-glucopyranoside of melting point 144.5-145.5°C. and a specific optical rotation of +82.0° (c = 2, chloroform) (27). Therefore, these results indicate that the three benzoate esters were substituted on the 2, 3, and 6 carbons and that the bromide group was present on the lactol carbon. The results also indicate that the original glucosyl halide had a pyranose configuration.

PHYSICAL PROPERTIES

The crystalline 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide had a specific optical rotation of +181.3° (c = 1, chloroform). In accordance with Hudson's rules of isorotation, the high positive rotation indicates an alpha or cis configuration of the glucosyl bromide. This indication is in agreement with the accepted stable configuration for glucosyl halides as proposed by Hassel and Ottar (28).

These data, therefore, confirm the premise that 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide can be prepared by brominating 1,2,3,6-tetra-O-benzoyl-D-glucose with titanium tetrabromide, and thus present a technique for preparing a bifunctional glucose molecule which theoretically should undergo polycondensation to yield the cellodextrin series.

ATTEMPTED POLYCONDENSATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

Eleven attempts were made to polycondense the 1-4 bifunctional glucose molecule employing a variety of conditions. These conditions and results are shown in Table III.

The only reactions in which a disaccharide could be identified in more than trace amounts are Nos. 5 and 11. The presence of gentiobiose in the products from reaction No. 5 is probably a result of the loss of a benzoate ester from the C-6 hydroxyl or due to an acyl migration from C-6 to C-4; however, the latter is probably the least probable since most acyl migrations are away from the lactol carbon. The fact that some β 1→4 condensation was attained at 25°C. and none at higher temperatures may be due to a shift in the equilibrium with temperature. It appears from Table III that mercuric cyanide is the most favorable catalyst for synthesizing 1→4 linked oligosaccharides as indicated by reaction No. 11, although the 1→4 linkage is of the alpha type.

These results show that under the wide variety of conditions used 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide will not undergo appreciable polycondensation to form the cellodextrin series of oligosaccharides.

TABLE III

ATTEMPTS TO POLYCONDENSE
2,3,6-TRI-O-BENZOYL-α-D-GLUCOSYL BROMIDE

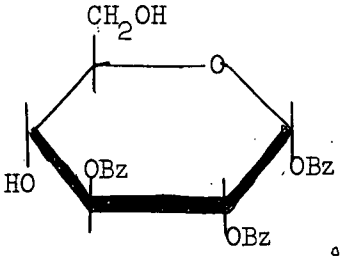
Reaction No.	Total Hours of Reaction	Temp. of Reaction, °C.	Acid Acceptor	Solvent[b]	Debenzoylated Products[a]
1	168	-5	Ag_2O	Chloroform	Glucose
2	168	-5	Ag_2O	Dimethyl formamide	Glucose
3	168	-5	Ag_2O	Pyridine	Glucose
4	168	-5	$Hg(OAc)_2$	Chloroform	Glucose
5	72	25	Ag_2O	Chloroform	Arabinose, glucose, cellobiose, gentiobiose, and several unidentified spots
6	8	60	Ag_2O	Chloroform	Glucose
7	24	60	Ag_2O	Chloroform	Glucose
8	8	60	Ag_2O	Dimethyl formamide	Glucose
9	8	60	$Hg(CN)_2$	Nitromethane	Glucose
10	24	60	$Hg(CN)_2$	Nitromethane	Glucose
11	8	72	$Hg(CN)_2$	Chloroform	Glucose, maltose, maltotriose

[a] As identified by paper partition chromatography.

[b] Concentrations in all the experiments were similar.

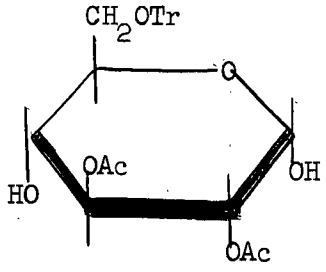
Since there are two functional groups on 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide, a C-4 hydroxyl and a C-1 bromide group, the failure to undergo polycondensation must be due to a low reactivity of one or both of these groups. It was suspected that actually both groups were of a low reactivity. The bromide group was thought to be relatively inactive due to steric hindrance from the large benzoate ester blocking groups, but this is not the case as will be shown later in this dissertation.

Since this dissertation was begun, several investigators have reported work which demonstrates that the C-6 hydroxyl has a much greater reactivity than the C-4 hydroxyl. Klemer (29) has shown that tetra-O-acetyl-α-D-glucosyl bromide when condensed with 1,2,3-tri-O-benzoyl-D-glucose (V) yields only gentiobiose (1→6 linkage) and no cellobiose (1→4 linkage).

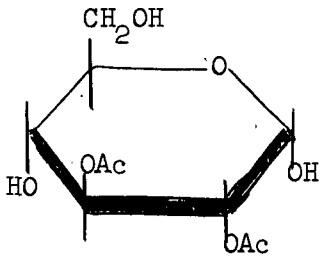


1,2,3-tri-O-Benzoyl-D-glucose (V)

Similarly, Rogovin and Novikova (30) attempted to condense tetra-O-acetyl-α-D-glucosyl bromide with 2,3-di-O-acetyl-6-O-trityl-D-glucose (VI) and 2,3-di-O-acetyl-D-glucose (VII) and obtained only what they thought was gentiobiose from the latter case. In no reaction could they obtain cellobiose.



2,3-di-O-Acetyl-6-O-trityl-D-glucose (VI)



2,3-di-O-Acetyl-D-glucose (VII)

It thus appears that the lack of polycondensation was due to a low reactivity of the C-4 hydroxyl group. To demonstrate that the C-4 hydroxyl group was the only inactive functional group, a study was made of the relative reactivity of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide under conditions of solvolysis. This comparison would demonstrate whether or not the lack of appreciable polycondensation could be partially attributed to a low reactivity of an O-benzoyl-α-D-glucosyl bromide relative to an O-acetyl-α-D-glucosyl bromide.

SOLVOLYSIS REACTIONS

The purpose of this phase of the dissertation was to make a comparison of the reactivity of the bromide groups of 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide, 2,3,4,6-tetra-O-benzoyl-α-D-glucosyl bromide and 2,3,4,6-tetra-O-acetyl-α-D-glucosyl bromide. It was suspected that the large benzoate esters might have caused a decrease in reactivity due to steric hindrance relative to acetate-substituted glucosyl halides. This comparison of rates of reaction was intended to determine whether or not the lack of condensation was due to this factor. Before such a comparison is

made between the rate constants of the acetates and benzoates, it is necessary to show that the two types of halides follow the same reaction mechanism.

NUCLEOPHILIC SUBSTITUTION REACTIONS

In nucleophilic substitution reactions a Lewis base using a pair of electrons forms a new bond to the carbon atom under attack, and the Lewis base originally bound to this carbon atom is freed, departing with the pair of electrons comprising the bond that has been broken. Equation (9) illustrates this type of reaction.

$$\underline{Y}:^- + \underline{R}:\underline{X} \longrightarrow \underline{Y}:\underline{R} + :\underline{X}^- \qquad (9)$$

Many investigators beginning with Hughes (31) have recognized that nucleophilic substitution reactions (S_n) could follow one of two types of mechanism, either bimolecular or unimolecular.

Bimolecular Reactions

In a bimolecular nucleophilic substitution (S_n2) reaction a new bond is being formed at the same time the old bond is breaking, and in the transition state the incoming group and outgoing group are both partially bonded to the carbon atom being attacked. The rate-controlling step of this reaction is shown in Equation (10).

$$\underset{\text{Reactants}}{\underline{Y}^- + \underline{R}:\underline{X}} \longrightarrow \underset{\text{Transition State}}{[\underline{Y}....\underline{R}....\underline{X}]^-} \longrightarrow \underset{\text{Products}}{\underline{Y}:\underline{R} + \underline{X}^-} \qquad (10)$$

Unimolecular Reactions

In a unimolecular nucleophilic substitution reaction (S_n1); the bond to the leaving group is broken before the new bond is created and the reaction proceeds through an intermediate of somewhat the same nature as a free carbonium ion. The rate-controlling step of this reaction is illustrated in Equation (11). The S_n1 reaction is synonymous with dissociation, heterolysis and solvolytic displacement reactions.

$$\underline{R}:\underline{X} \longrightarrow \underline{R}^{+}+\underline{X}:^{-} \qquad (11)$$

Transition State

ANALYSIS OF REACTION MECHANISM

When S_n reactions are conducted under conditions of solvolysis, i.e., where the Lewis base is in large excess, both S_n1 and S_n2 reactions follow first order kinetics because the concentration of Lewis base remains essentially constant. Therefore, kinetic order is not diagnostic of mechanism. For solvolytic reactions, another type of mechanistic analysis must be initiated.

The following analysis of nucleophilic substitution reactions originated with Hughes (31). The analysis is based on six factors which affect the rate of unimolecular and bimolecular reactions.

Electron Accession to the Seat of Substitution

Accession of electrons to the seat of substitution slightly decelerates a bimolecular reaction while a unimolecular reaction will be

strongly accelerated. An exception to this effect is the transition region between S_n1 and S_n2.

Nucleophilic Nature of the Substituting Reagent

Addition to the reaction medium of a stronger Lewis base should not alter the rate of an S_n1 reaction since it does not participate in the rate-controlling stage; however, small changes in rate may be noticed due to changes in ionic strength and/or dielectric constant. An S_n2 reaction should be greatly accelerated due to the presence of a more nucleophilic group since it participates in the rate-determining stage.

Ionizing Power of the Solvent

Increasing the ionizing power of the reaction medium should increase the rates of both S_n1 and S_n2 reactions; however, as the ionizing power of the medium increases, the S_n1 reaction should gain in importance.

Stereochemical Course of the Reaction

It has previously been mentioned that in S_n2 reactions the nucleophilic group attacks the carbon atom from one side, while the leaving group departs from the opposite side. The net stereochemical result for an S_n2 reaction should be, therefore, complete inversion of configuration.

The intermediate step in S_n1 reactions approximates a free carbonium ion and the nucleophilic group should have an equal possibility of attacking either side. The net stereochemical result should be a racemic mixture.

Kinetic Form of the Substitution Reaction

The unimolecular reaction will show substantial departure from first order kinetics if the dissociation step is assumed to be significantly reversible. This can be expressed mathematically as follows if it is assumed that the ionization step is reversible and the concentration of Y remains essentially constant.

$$\underline{R}:\underline{X} \underset{\underline{k}_r}{\overset{\underline{k}_f}{\rightleftharpoons}} \underline{R}^+ + \underline{X}:^- \qquad (12)$$

$$\underline{R}^+ + :\underline{Y}^- \xrightarrow{\underline{k}'} \underline{R}:\underline{Y} \qquad (13)$$

$$\text{Over-all rate of reaction} = \underline{k}_f(\underline{R}:\underline{X}) \,/\, [1+(\underline{k}_r(:\underline{X}) \,/\, \underline{k}')] \qquad (14)$$

where, $\underline{k}_f$ is the specific rate constant for the forward ionization reaction,

$\underline{k}_r$ is the specific rate constant for the reverse ionization reaction, and

$\underline{k}'$ is the specific rate constant for the fast second step of the reaction.

It can be seen from this equation that a departure from first order kinetics should be expected for an S_n1 reaction unless the ratio $\underline{k}_r(:\underline{X}) \,/\, \underline{k}'$ is small compared with unity. If $\underline{k}_r(:\underline{X}) \,/\, \underline{k}'$ is appreciable, a mass-law effect should be noted; that is, as the reaction progresses, the build-up of the $:\underline{X}^-$ in the solution should cause a suppression of the ionization step with a resultant decrease in the rate of reaction.

Bimolecular reactions, on the other hand, should consistently follow first order kinetics where nucleophilic reagent is in large excess.

Effects of Added Salts

The addition of salts to the reaction medium can have three possible effects on the rate of reaction. These effects can be classified as (1) a mass-law effect, (2) an ionic strength or salt effect, and (3) increasing the ionizing power of the medium.

The mass-law effect occurs when a neutral salt with a common anion is added to the reaction. The mass-law dictates that if the ratio $k_r(:X) / k'$ in Equation (14) is significant, addition of the common anion should cause a retardation of the over-all rate of a unimolecular reaction. On the other hand, an S_n2 reaction should suffer no such mass-law retardation.

The salt effect is a result of an electrostatic interaction of charges which results in a change in the activity coefficients of the species present. Therefore, if activity is the driving force for the reaction, the rate of reaction is altered. Experimentally, it has been found for the aliphatic series of halides that this effect is opposite to the mass-law effect and is more pronounced for unimolecular than bimolecular reactions.

It should also be mentioned that the mass-law effect and salt effects are usually superimposed.

The third effect of adding salts to a reaction medium is that of increasing the ionizing power of the medium. This effect is quite similar to that of increasing the dielectric constant of the reaction because it

allows for separation of charge stabilized by an ionic atmosphere and thus increases the rate of a unimolecular reaction to a greater extent than a bimolecular reaction.

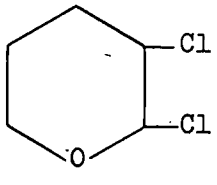
REACTIVITY OF O-ACETYL GLYCOSYL HALIDES

Newth, Phillips, et al. (32-34) have conducted an extensive investigation for the solvolysis of O-acetyl glycosyl halides using the previously described mechanism analysis of Hughes (31). This analysis will be described below.

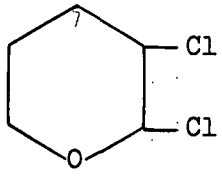
Electron Accession to the Seat of Reaction

Although it is impossible to measure quantitatively the ability of a given group or atom to release electrons to the seat of reaction, it is of interest to compare qualitatively the electron-releasing capacity of various groups and atoms.

Newth and Phillips (32) have studied the hydrolysis of 2,3-dichlorotetrahydropyran (VIII) and 2,3-dichloro-thiacyclohexane (IX) to assess the extent to which the lactol ring oxygen atom promotes C-halogen bond fission. Their study showed the tetrahydropyran to be more hydrolyzable



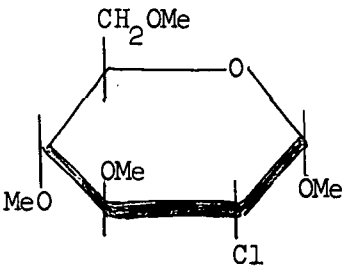
2,3-Dichloro-
tetrahydropyran (VIII)



2,3-Dichloro-
thiatetrahydropyran (IX)

than the thiacyclohexane. This difference can be attributed to the greater electron-releasing capacity of oxygen compared with sulfur. By analogy, they concluded that O-acetyl glucosyl bromide followed an S_n1 course of solvolysis because the halide is also an alpha-halogeno ether system and allowed fission of the C-halogen bond.

Further evidence as to the participation of the ring oxygen in reactivity was gained by an attempt to react methyl 2-chloro-2-deoxy trimethyl-D-glucoside (X) with methanol. This attempt showed the chlorine not adjacent to the lactol ring oxygen to be almost completely unreactive.



Methyl 2-chloro-2-deoxy
trimethyl-D-glucoside (X)

Nature of Nucleophilic Group

The rate of hydrolysis of tetra-O-acetyl-α-D-glucosyl bromide was not significantly changed by conducting reactions in two different concentrations (0.025M and 0.075M) of sodium hydroxide. Since such a powerful nucleophilic reagent did not alter the rate of reaction, it was concluded that the reaction must be unimolecular. This hypothesis is based on the assumption that concentration and not activity is the driving force for the reaction. This assumption is probably valid considering the good fit their plot of concentration versus time shows to first-order kinetics.

Ionizing Power of the Solvent

Increasing the amount of water in a methanol-water solution from 0 to 40% caused a 13-fold increase in the specific rate constant. In a similar manner, increasing the per cent water from 10 to 40% in a water-acetone medium caused a 29-fold increase in the specific rate constant. Both of the changes in water increase the dielectric constant and because of the magnitude of the change suggest that an S_n1 mechanism is occurring.

Stereochemical Course of the Reaction

The stereochemical course of substitution reactions of glycosyl halides appears to be in direct conflict with what would be expected for S_n1 and S_n2 reactions. The experimental evidence to date indicates a unimolecular mechanism for cis-acetyl-glycosyl halides. However, cis-acetyl-glycosyl halides give complete inversion of configuration in solvolysis reactions; whereas theoretically a racemic mixture would be expected. The reason that complete inversion is attained while following an S_n1 mechanism is that the attacking nucleophile reacts so rapidly that the departure of the halide acts as a steric hindrance to the approach of any reagent from that side. Also the cis blocking group on C-2 may somewhat shield the carbonium ion from that side.

Kinetic Form of the Substitution Reaction

The hydrolysis and methanolysis of cis-acetyl-glycosyl halides follow first-order kinetics for at least the first 50% of the reaction after

which a slight increase in the rate of reaction is noted. Newth and Phillips (32) suggest that this increase in rate of reaction is due probably to an acid-base catalysis and also to an increase in the ionizing power of the medium from the liberated hydrogen bromide. There probably is also a negligible mass-law effect superimposed on the rate curve.

Effects of Added Salts

The addition of neutral bromide salt (0.04M LiBr) caused a 5% increase in the rate of reaction. This result is probably due mainly to the increase in ionizing power of the media and suggests that, if the reaction is unimolecular, the reverse ionization step is negligible. This small salt effect also helps substantiate the fact that the driving force for the reaction is concentration.

Based on the previous evidence it appears, therefore, that the solvolysis (hydrolysis and methanolysis) of tetra-acetyl-α-D-(cis)-glucosyl bromide follows a unimolecular path of reaction and that the reverse ionization step is essentially negligible.

MECHANISM OF SOLVOLYSIS OF O-BENZOYL GLUCOSYL BROMIDES

Since no extensive work has previously been conducted to study the reaction mechanism of the solvolysis of O-benzoyl glucosyl halides, it was found necessary to determine its characteristics experimentally. According to the previous discussion, probably the single most effective

factor distinguishing unimolecular and bimolecular substitution reactions is the dependence of the rate of reaction on the Lewis base strength of the substituting reagent. This technique was used to demonstrate that 2,3,4,6-tetra-O-benzoyl-α-D-glucosyl bromide and 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide follow the same unimolecular pathway as does 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. The data for solvolysis reactions are shown in Table IV.

TABLE IV

THE EFFECT OF LEWIS BASE STRENGTH ON RATES OF REACTION

Temperature = 33.4°C.

Lewis Base	Rate Constant of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide, $sec.^{-1}$	Rate Constant of 2,3,4,6-tetra-O-Benzoyl-α-D-glucosyl Bromide, $sec.^{-1}$
Water	32.5×10^{-5}	15.7×10^{-5}
Methanol	37.0×10^{-5}	11.0×10^{-5}
Ethanol	30.0×10^{-5}	9.4×10^{-5}

The semilogarithmic plots of $\alpha_t - \alpha_\infty$ *versus* time from which the rate constants can be determined are shown in Fig. 3-7. The actual data from which these graphs were determined are given in Appendix II.

In all cases of solvolysis dimethyl formamide was used as a non-reactive polar solvent containing from 10 to 20% by volume of Lewis base. It should be noted that it is usually considered that at least a 10-fold difference in rate constant must be demonstrated before it is considered

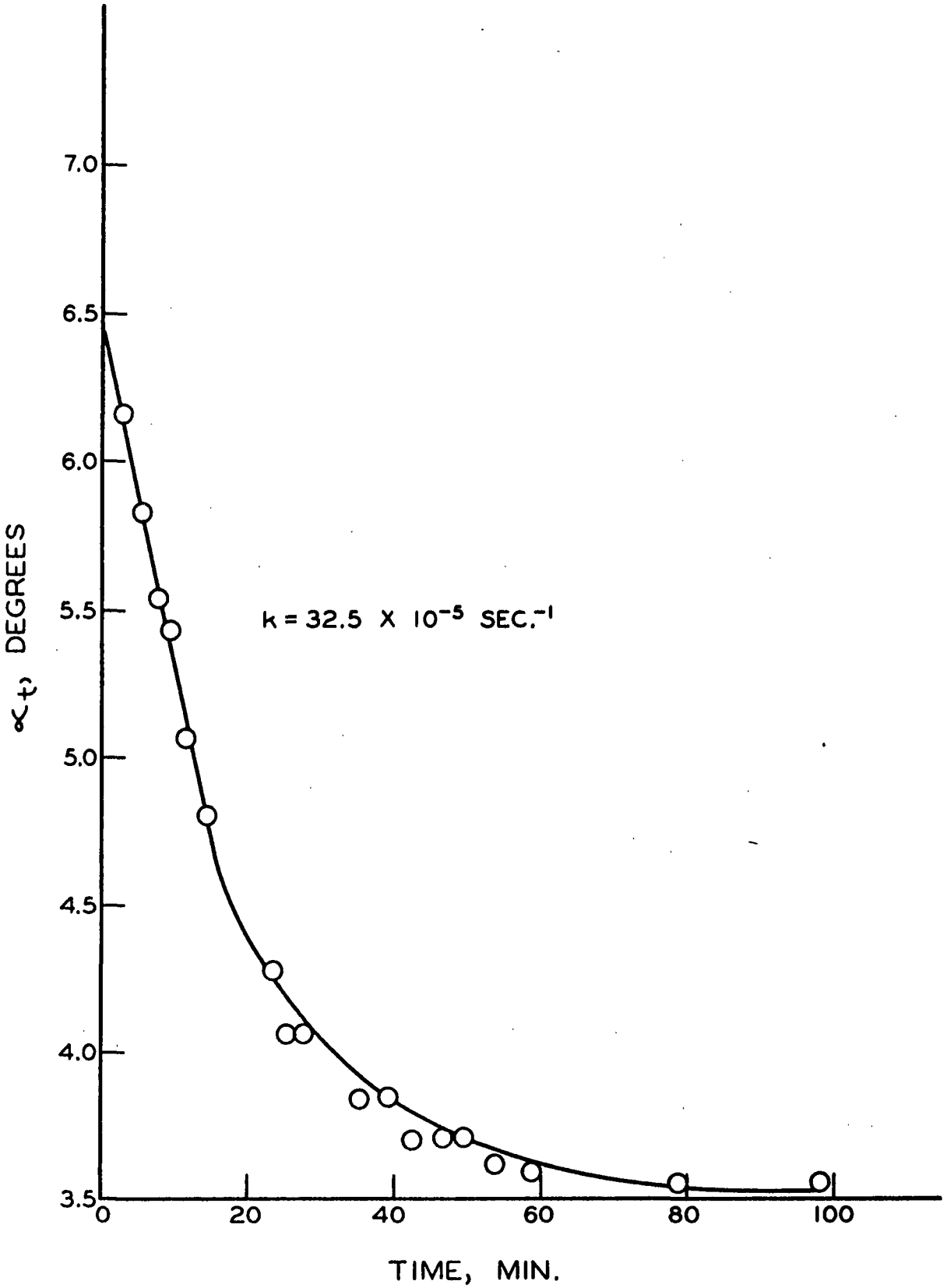


Figure 3. Hydrolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide in Water:DMF (12:88) at 33.4°C.

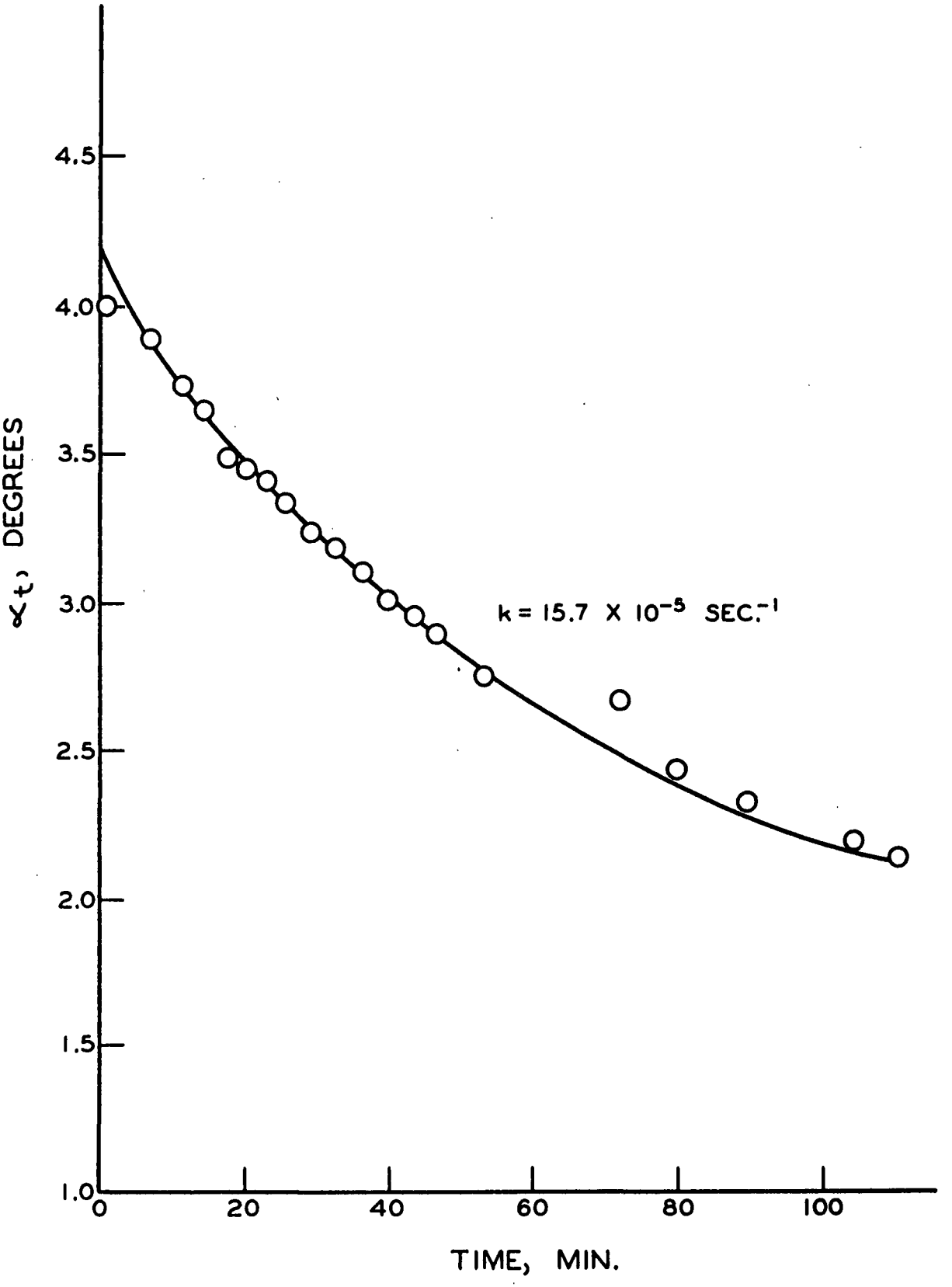


Figure 4. Hydrolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide in Water:DMF (12:88) at 33.4°C.

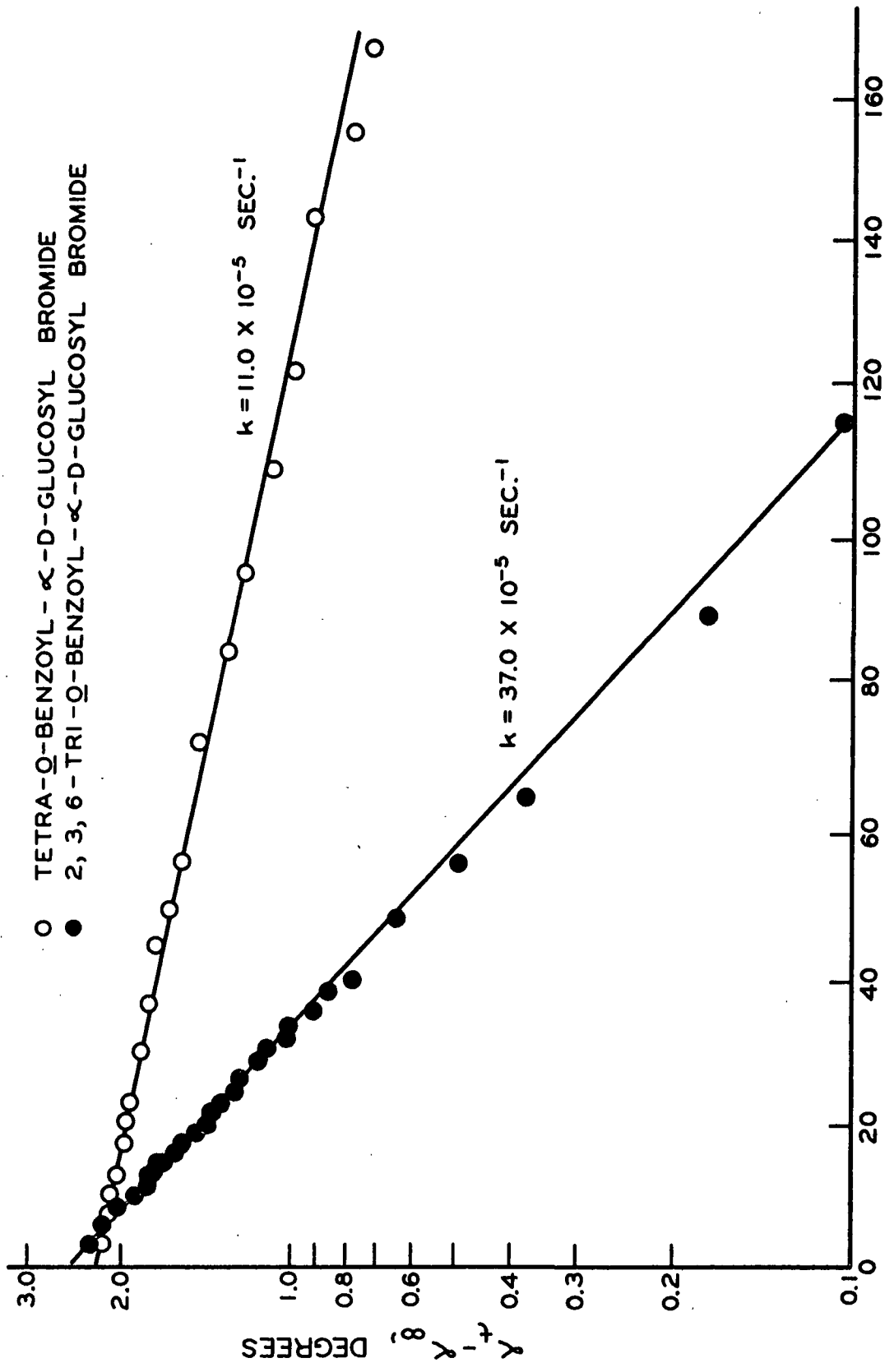


Figure 5. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides in Methanol:DMF (12:88) at 33.4°C.

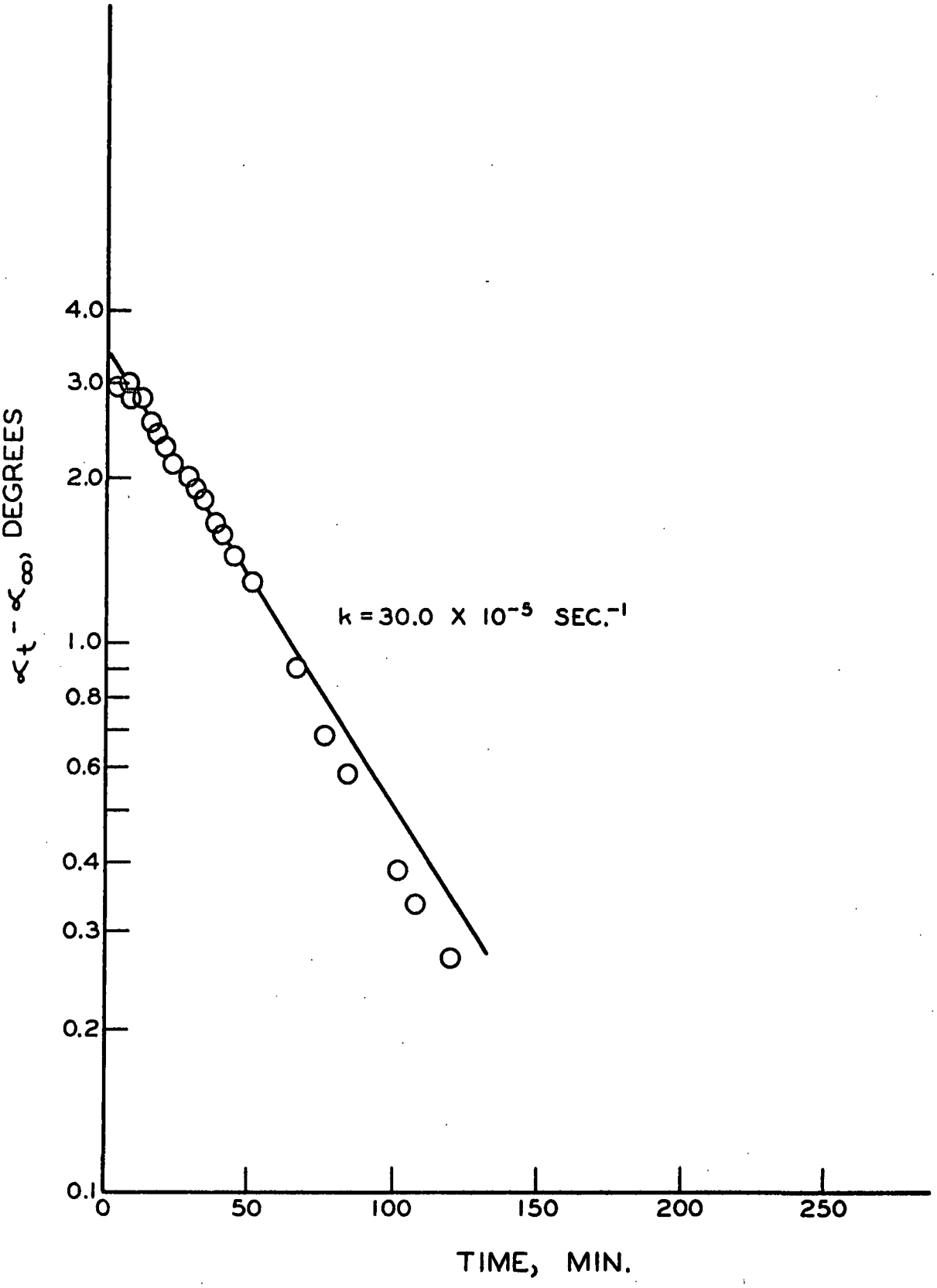


Figure 6. Ethanolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide in Ethanol:DMF (2:8) at 33.4°C.

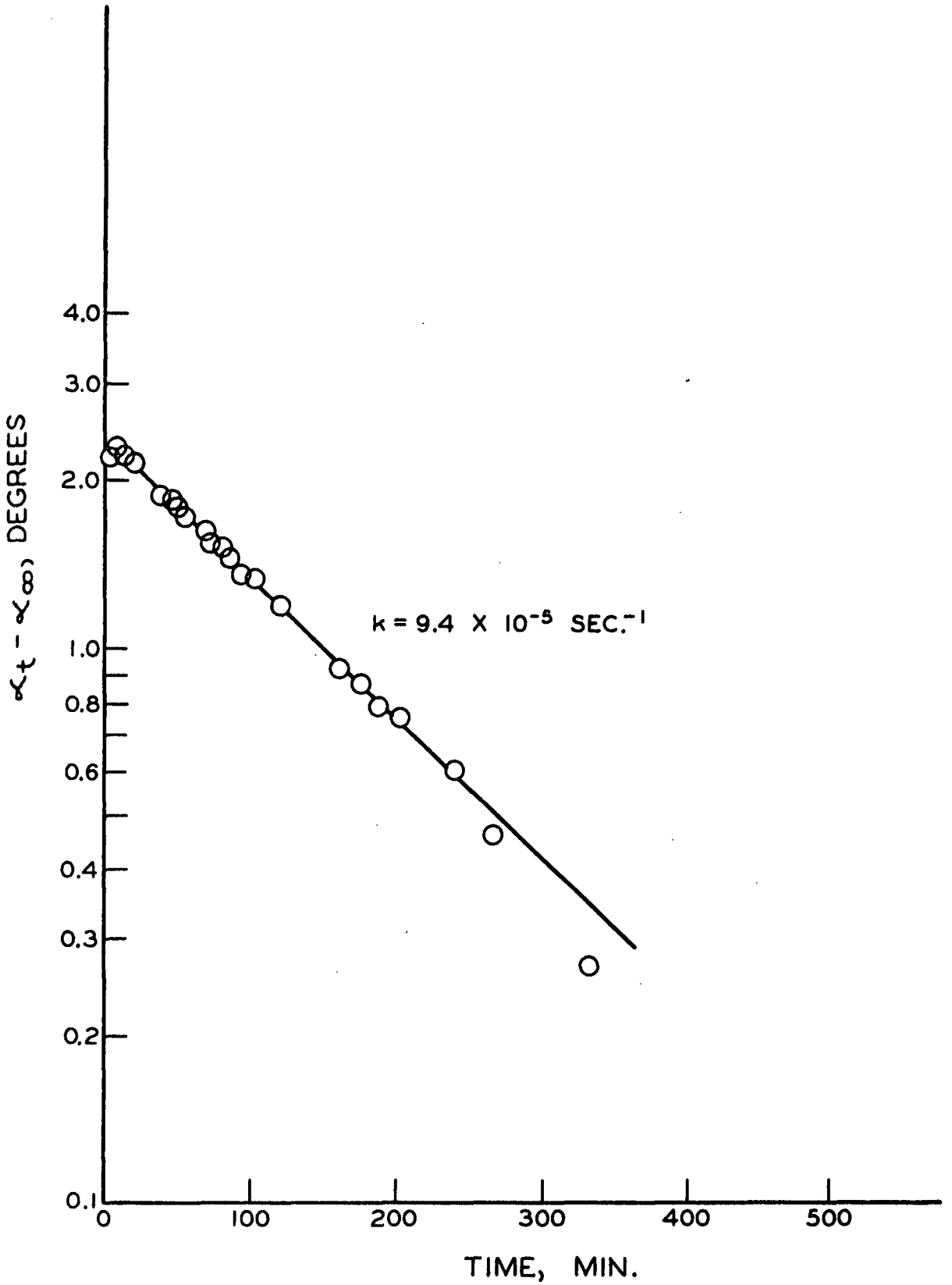


Figure 7. Ethanolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide in Ethanol:DMF (2:8) at 33.4°C.

that a significant difference exists in the rate constant. The maximum error in estimating these rate constants from the slopes of $\ln(\alpha_t - \alpha_\infty)$ *versus* time was 10%. The apparent consistency of the rate constants as a function of Lewis base strength is good evidence that both of the benzoyl glucosyl bromides follow a unimolecular path. According to Swain's (50) nucleophilicity parameter, *n*, the pure solvents have a value H_2O = -0.44; methanol = -0.05; ethanol = -0.53 where 80% ethanol:20% water has a value of 0.00.

Table V shows the activation energies for tetra-*O*-benzoyl and tetra-*O*-acetyl-α-D-glucosyl bromides for methanolysis in methanol:dioxane (9:1).

TABLE V

ACTIVATION ENERGIES

O-Acyl glucosyl halide	Activation Energies
Tetra-*O*-benzoyl-α-D-glucosyl bromide	19,100 ± 1000 cal./mole
Tetra-*O*-acetyl-α-D-glucosyl bromide	21,100 ± 1400 cal./mole

The close agreement of activation energies is again confirming evidence that the two types of glucosyl halides follow the same reaction mechanism.

Since strong evidence had been presented to indicate that *O*-acetyl and *O*-benzoyl glucosyl bromides undergo solvolysis by the same unimolecular mechanism, it was then possible to compare their reactivity.

COMPARISON OF THE REACTIVITY OF O-ACETYL GLUCOSYL BROMIDES AND O-BENZOYL GLUCOSYL BROMIDES

To compare the reactivity of the O-acetyl and O-benzoyl glucosyl bromides the initial rate constants were determined for all three compounds in an identical solvent. Methanol:dioxane (9:1) was chosen as the solvent system. Figures 8-16 are semilogarithmic plots of $\alpha_t - \alpha_\infty$ versus time for these solvolysis reactions from which the rate constants can be determined. It should be noted that in the two middle curves there is a break in the curve. In these two curves only the initial slope was used in determining rate constants. No explanation could be found for this break in the curve. Figure 17 is the semilogarithmic plot of k versus the reciprocal of the absolute temperature from which the activation energies can be calculated.

These plots show unexpectedly that the most reactive species is 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide, followed by 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide, and the slowest reacting compound is 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. These results were entirely unexpected since previous to this data it had always been accepted that O-acetyl glucosyl bromides were more reactive than O-benzoyl glucosyl bromides, based on the fact that acetate esters offer much less steric hindrance than do benzoate esters. However, this is the first concrete evidence that demonstrates to the contrary. It is possible that the greater reactivity of the O-benzoyl glucosyl bromides was due to solvation effects, i.e., the O-benzoyl glucosyl bromide is solvated better in methanol:dioxane (9:1) than O-acetyl

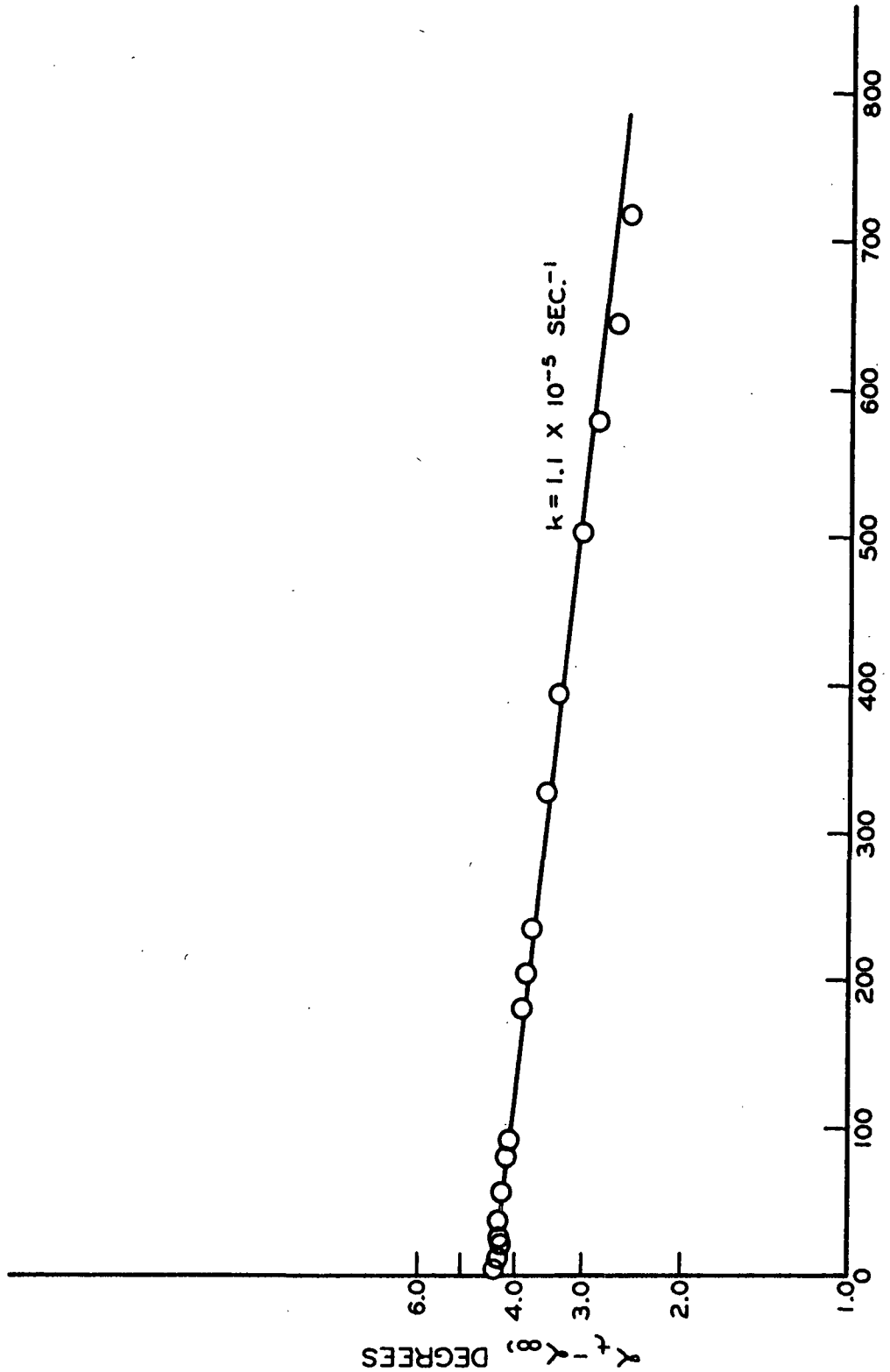


Figure 8. Methanolysis of tetra-O-Acetyl-α-D-glucosyl Bromide in Methanol:Dioxane (9:1) at 37.0°C.

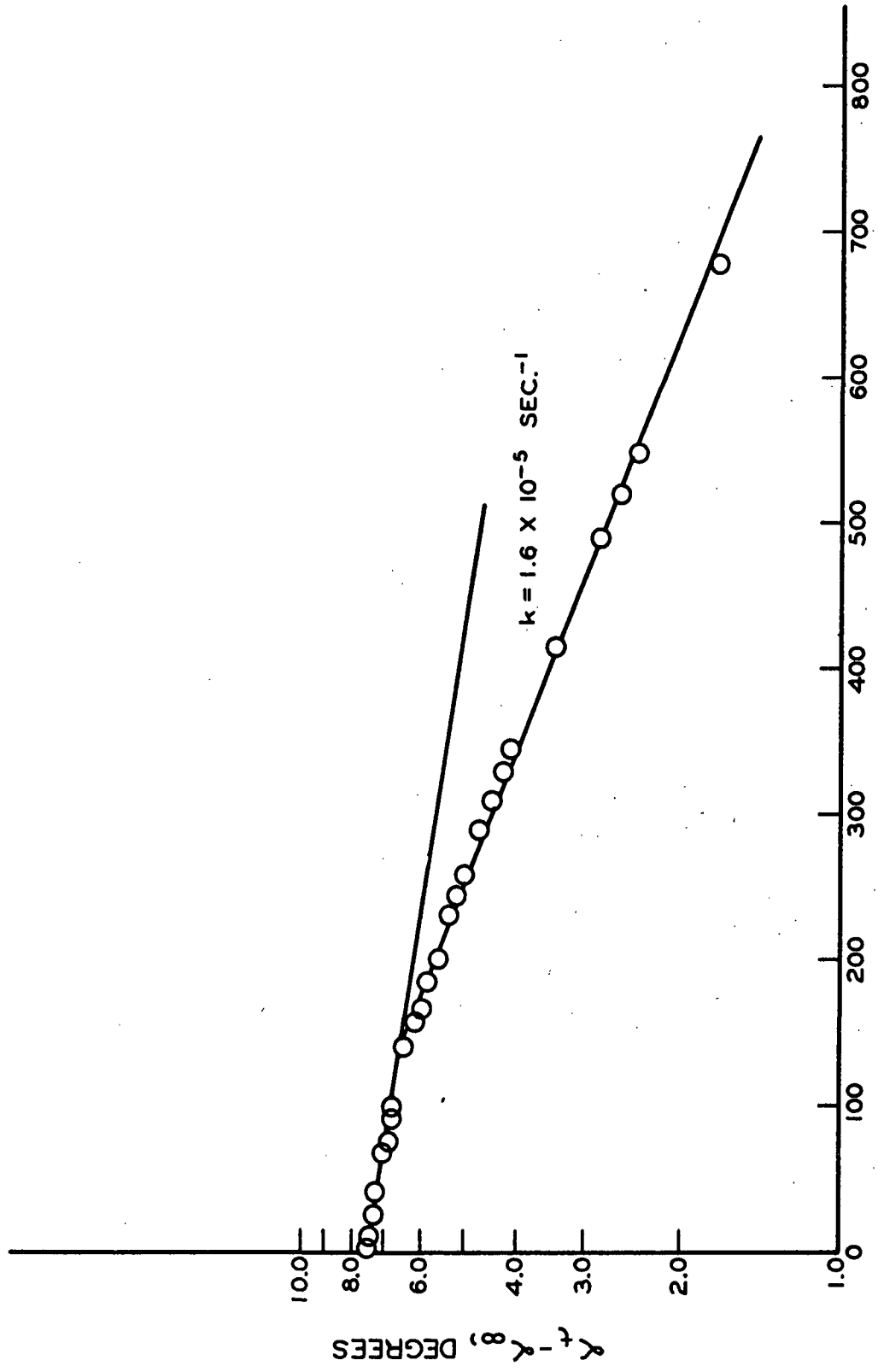


Figure 9. Methanolysis of tetra-O-Acetyl-α-D-glucosyl Bromide in Methanol:Dioxane (9:1) at 43.0°C.

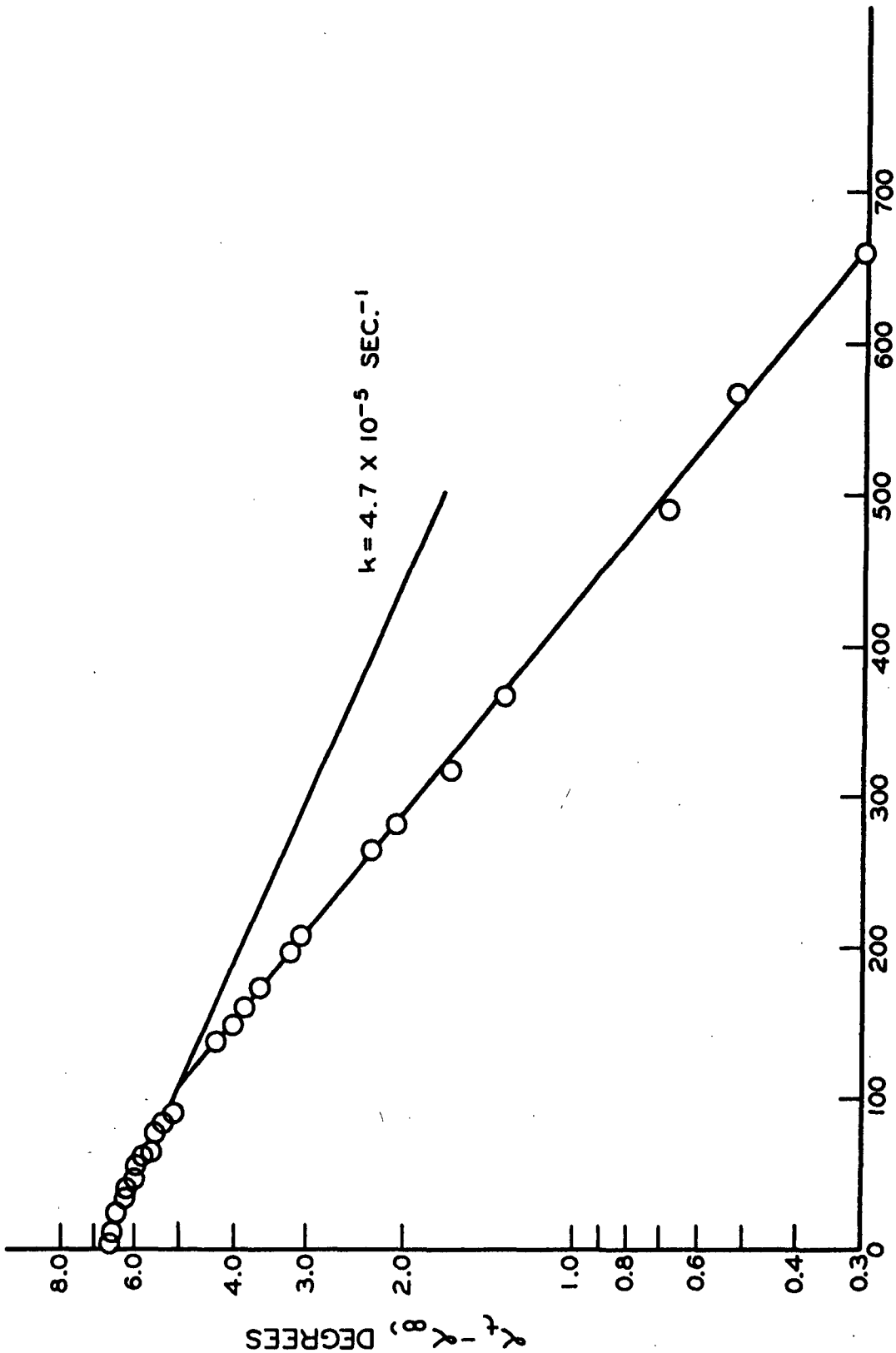


Figure 10. Methanolysis of tetra-O-Acetyl-α-D-glucosyl Bromide in Methanol:Dioxane (9:1) at 51.0°C.

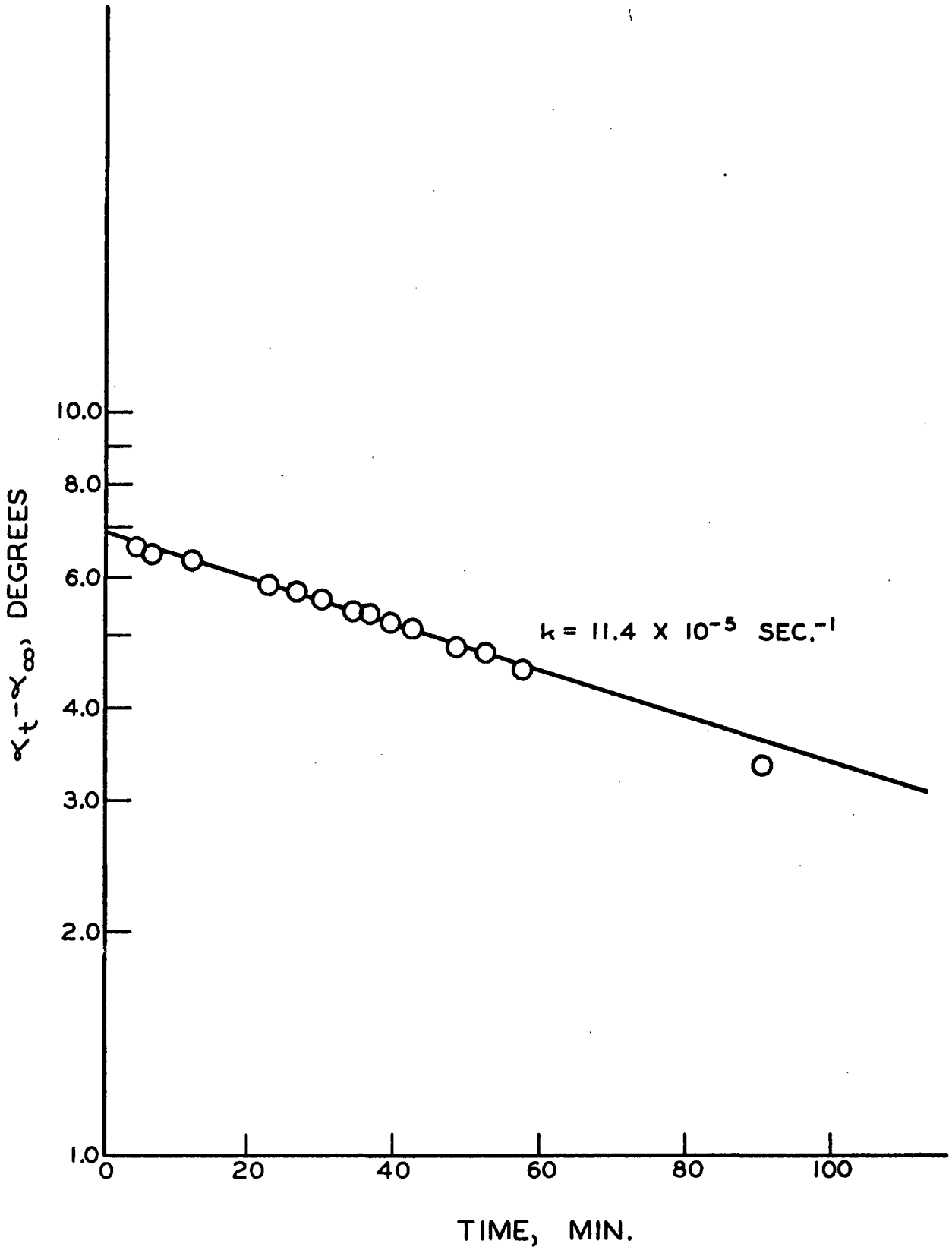


Figure 11. Methanolysis of tetra-O-Acetyl-α-D-glucosyl Bromide at 60.3°C. in Methanol:Dioxane (9:1)

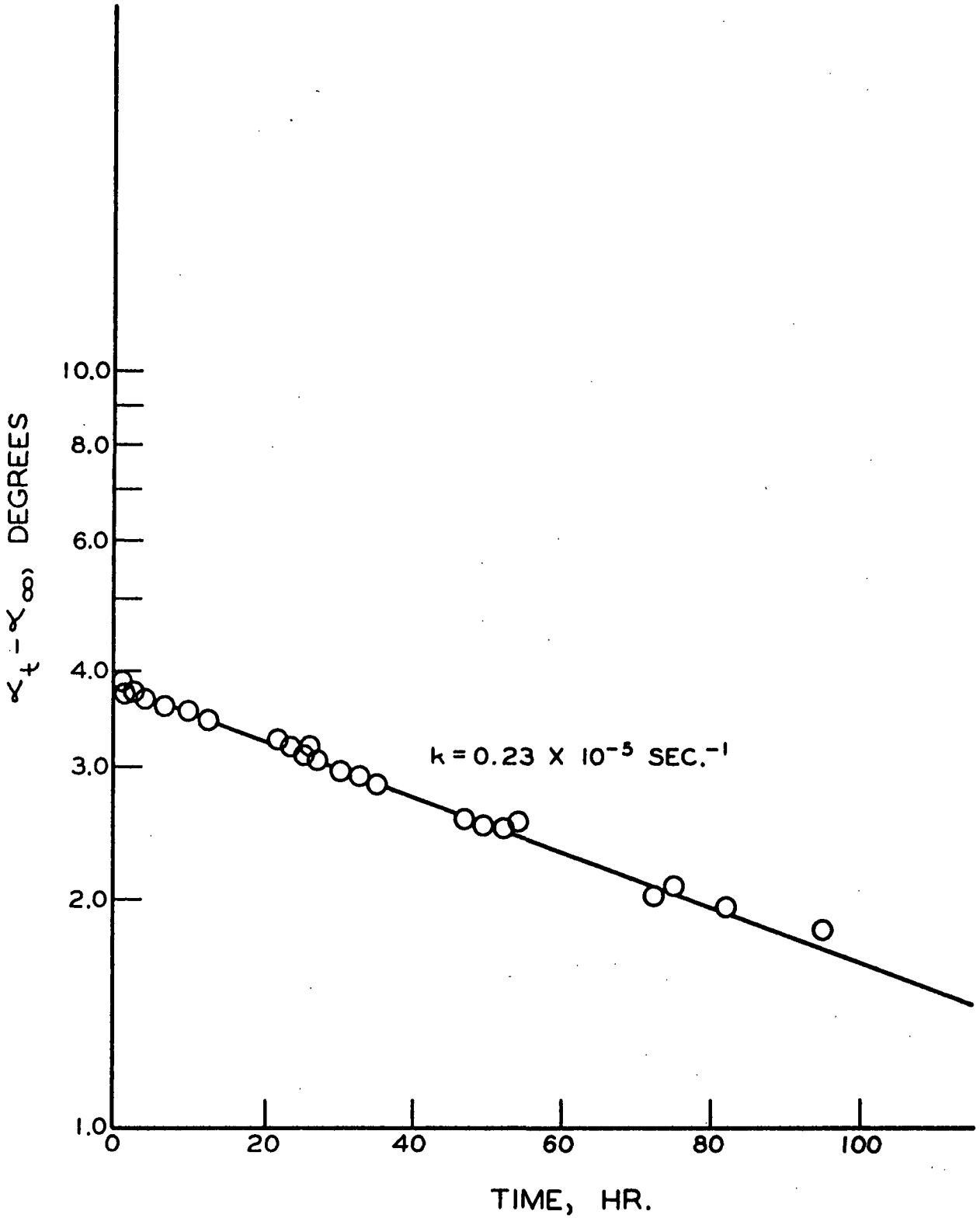


Figure 12. Methanolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide at 13.0°C. in Methanol:Dioxane (9:1)

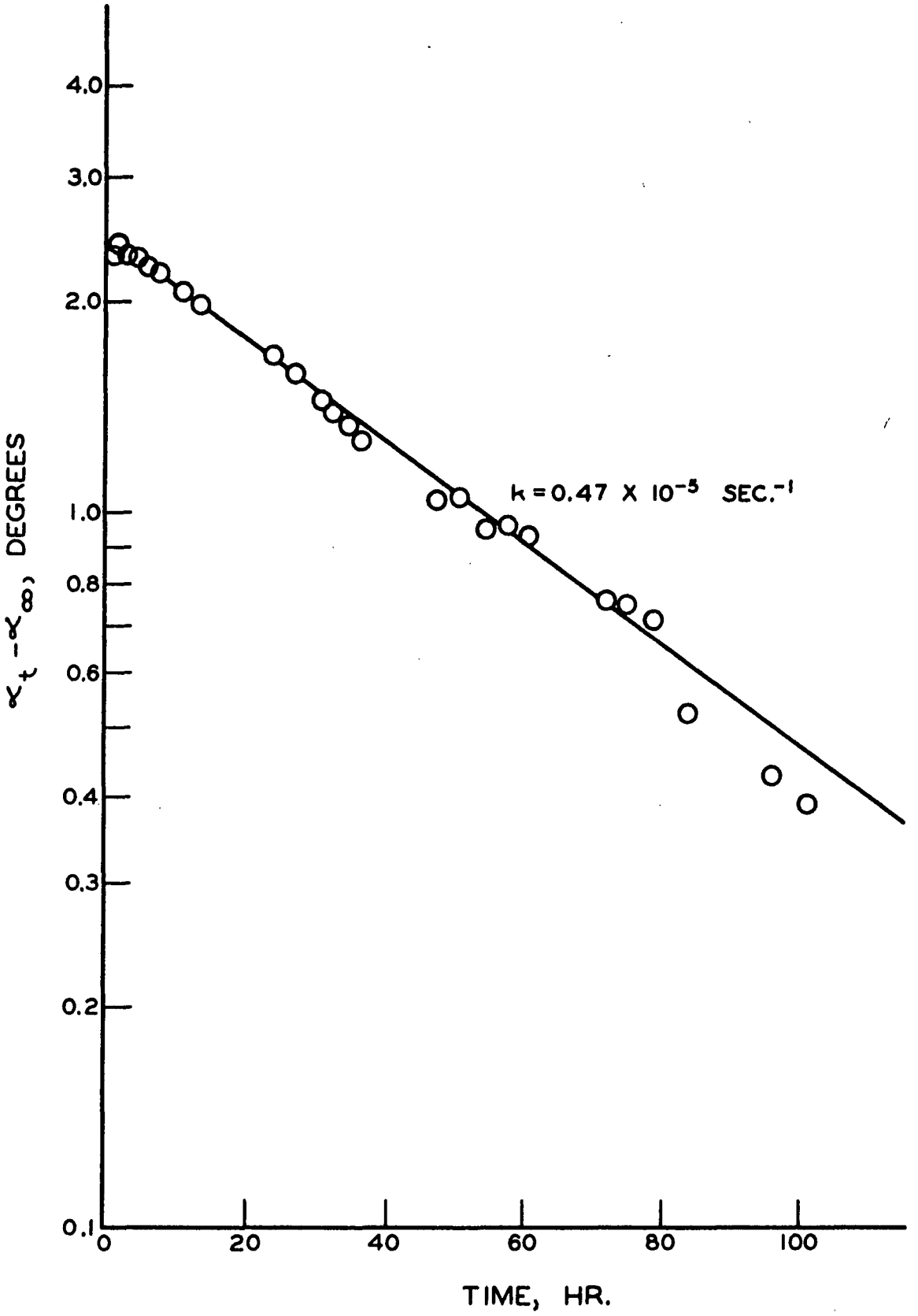


Figure 13. Methanolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide at 18.4°C. in Methanol:Dioxane (9:1)

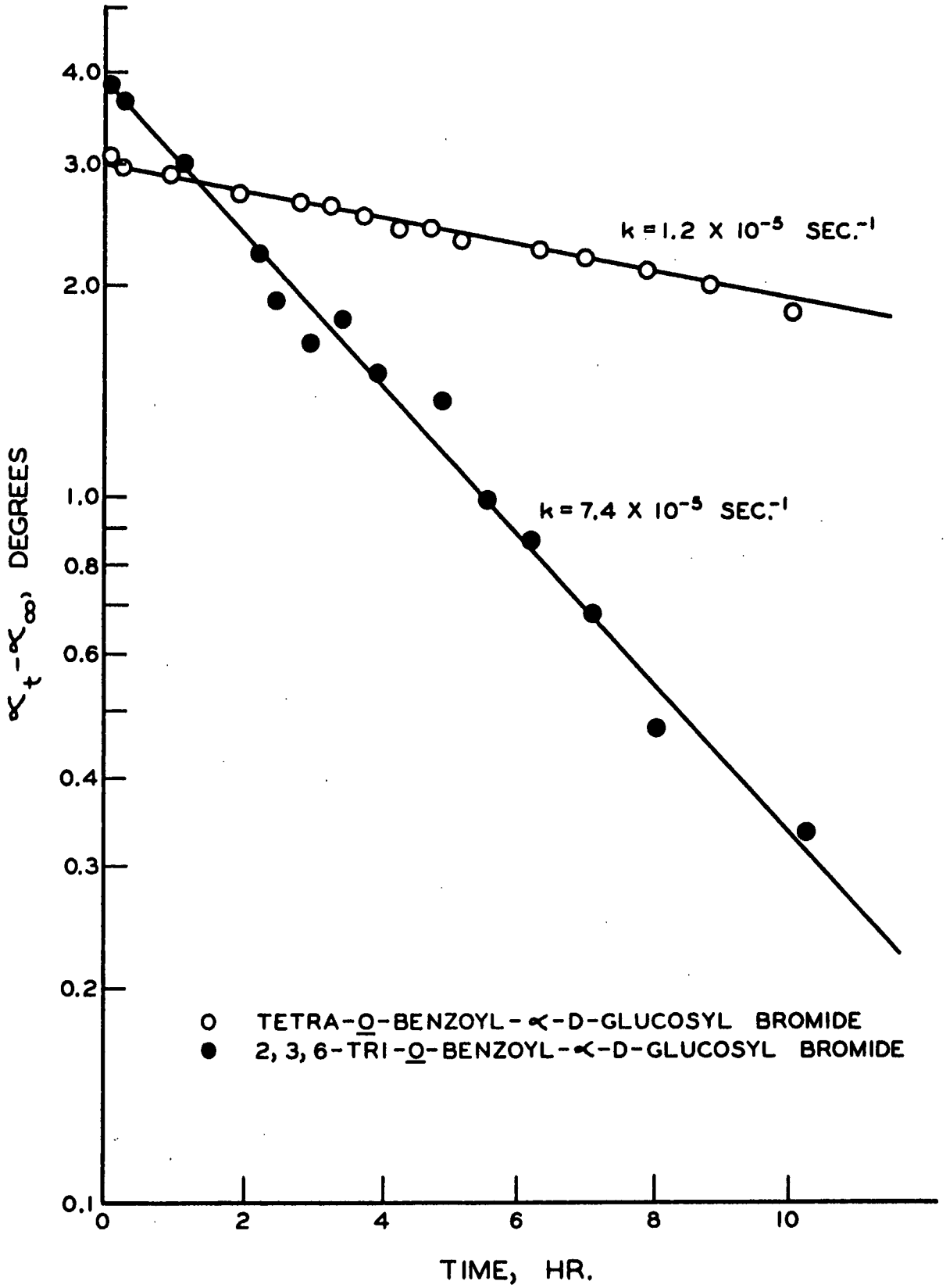


Figure 14. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides at 27.1°C. in Methanol:Dioxane (9:1)

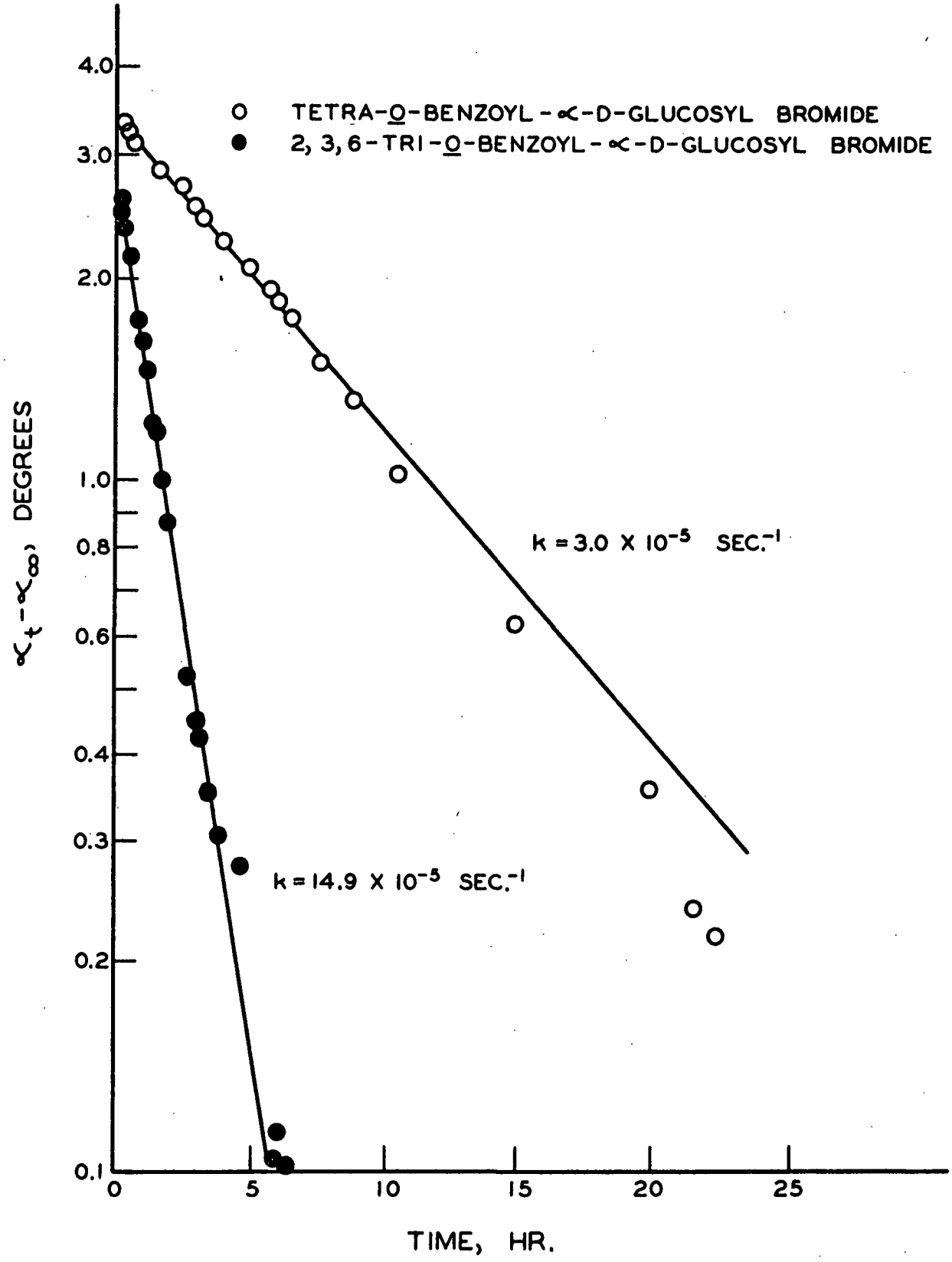


Figure 15. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides at 35.2°C. in Methanol:Dioxane (9:1)

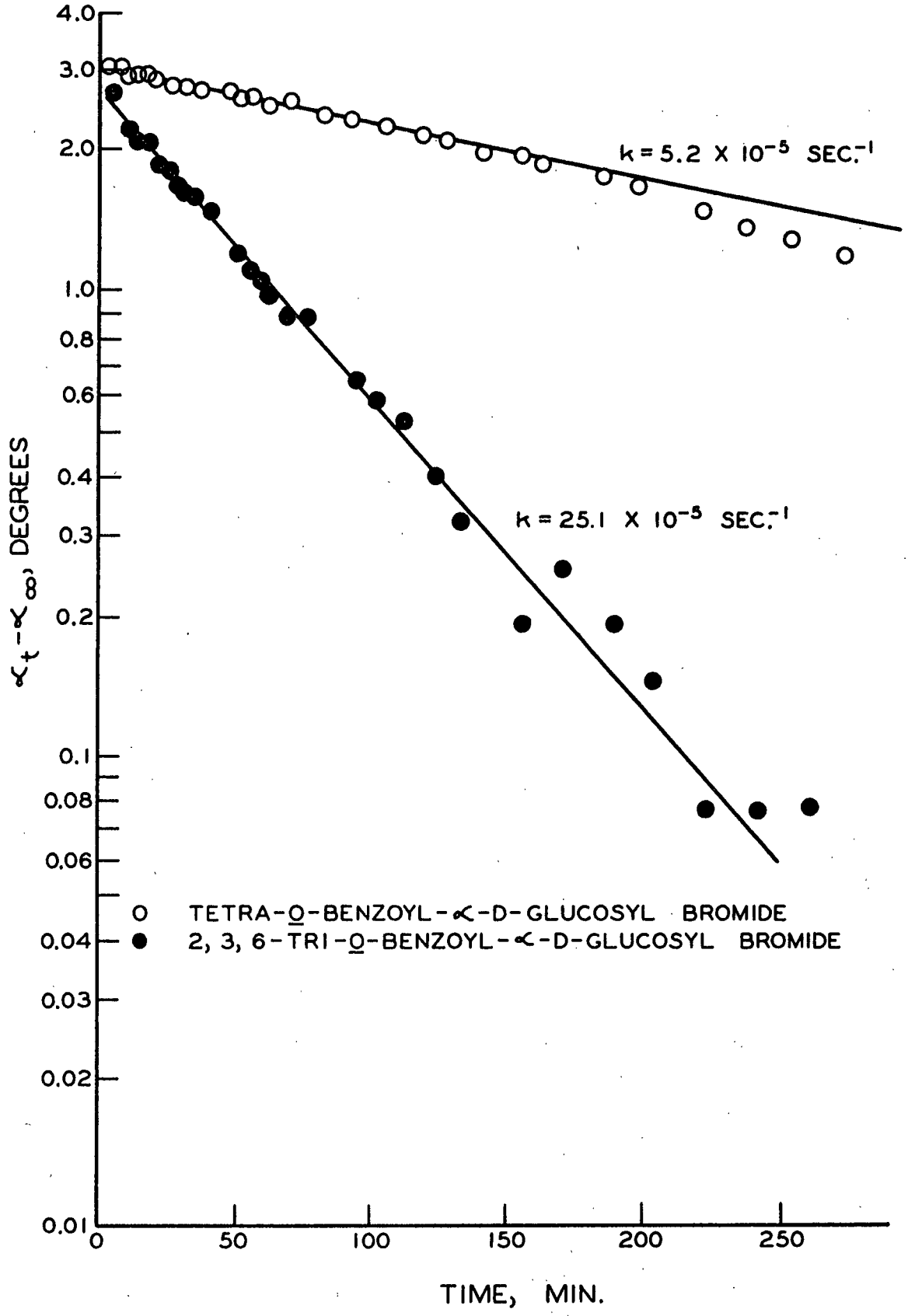


Figure 16. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides at 41.5°C. in Methanol:Dioxane (9:1)

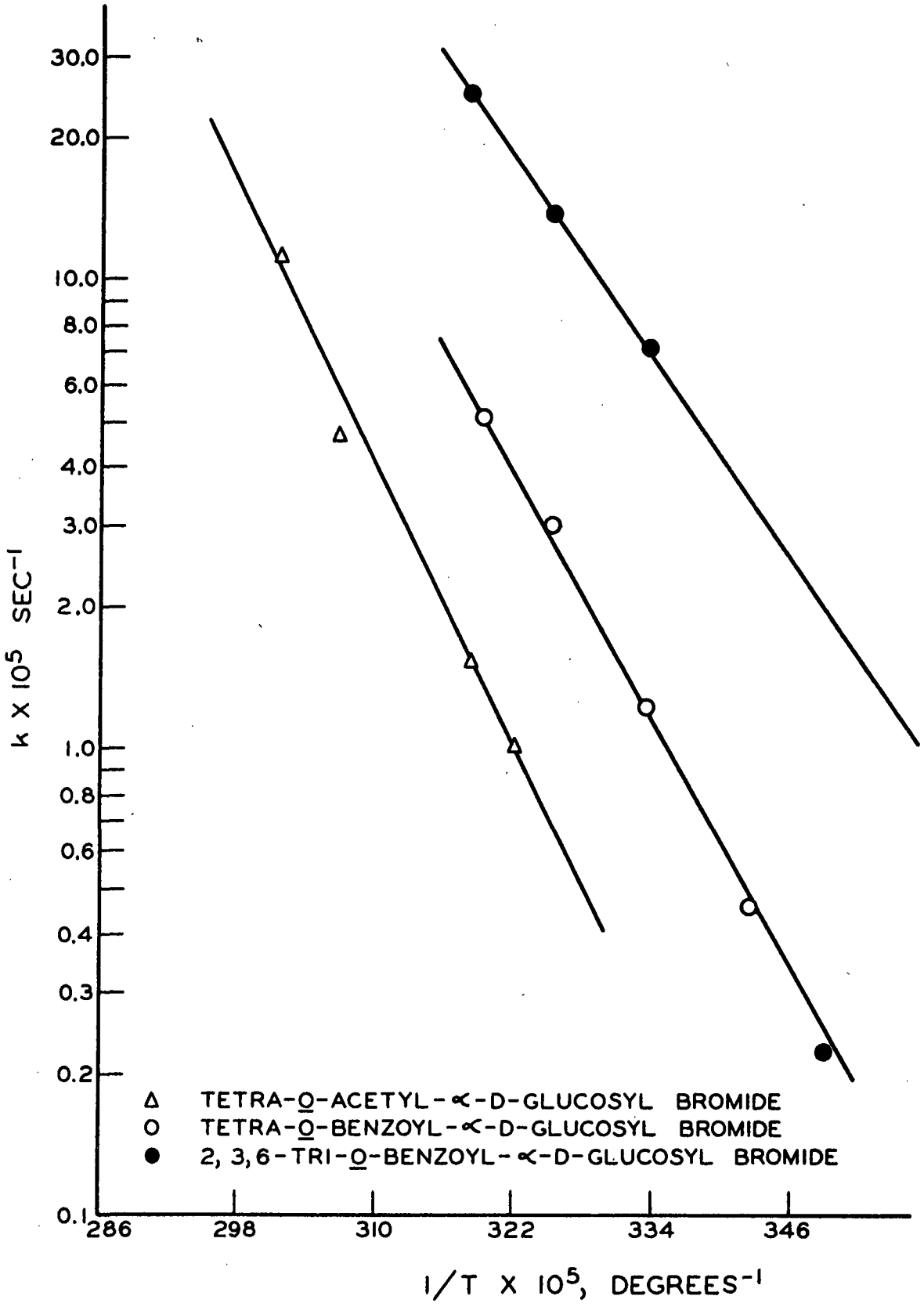


Figure 17. Variation of Rate Constants as a Function of Temperature for Methanolysis of O-Acyl glucosyl halides in Methanol:Dioxane (9:1)

glucosyl bromides, thus allowing a closer approach of the reactive solvent. If this hypothesis is true, it would be expected that the order of reactivity of the glucosyl halides might change with solvent systems, the O-acetyl glucosyl bromides being more reactive in the more polar solvents and the O-benzoyl glucosyl bromides being more reactive in less polar solvents. This type of study was not conducted because it was not considered pertinent to this dissertation. It was considered only important to demonstrate the similarity in the reactivity of O-benzoyl and O-acetyl-α-D-glucosyl bromides.

Since a 1-6 bifunctional acetate substituted glucose molecule underwent polycondensation, and a 1-4 bifunctional benzoate substituted glucose molecule did not undergo appreciable polycondensation, and since a benzoate substituted glucosyl halide is shown to be as reactive as an O-acetyl glucosyl halide, it was possible to conclude that the lack of condensation was due to a low reactivity of the C-4 hydroxyl alone. It should be noted that the above information does not indicate whether or not the reactivity of the C-4 hydroxyl group could be attributed to steric hindrance from the large benzoate esters.

CHARACTERIZATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

The purpose of this phase of the dissertation was to compare the reactivity of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide with tetra-O-benzoyl-α-D-glucopyranosyl bromide as a means of qualitatively estimating the effect of the C-4 benzoate ester on reactivity of the glucosyl

bromide. Rates of methanolysis measurements were made in two different nonreactive solvents, dioxane and dimethyl formamide, in which cases methanol was always present in large excess compared with the halide. Figures 8-16, 18-27 are the semilogarithmic plots of $\alpha_t - \alpha_\infty$ versus time for these reactions. The slope of these lines is equal to -k, the specific rate constant. Figures 17, 28 are semilogarithmic plots of k versus the reciprocal of the absolute temperature for these reactions. The activation energies calculated from Fig. 17 and 28 are shown in Tables VI and VII. The original data from which these plots were determined can be found in Appendix II. Sample calculations and the method of calculating the activation energies in Tables VI and VII can be found in Appendix III.

TABLE VI

ENERGIES OF ACTIVATION IN METHANOL:DIOXANE (9:1)
TEMPERATURE RANGE 12-42°C.

	2,3,6-tri-O-Benzoyl-α-D-glucosyl bromide	2,3,4,6-tetra-O-Benzoyl-α-D-glucosyl bromide
E_{exp}	16,400 ± 900 cal./mole	19,200 ± 1,000 cal./mole
ΔH^{*}	17,000 ± 900 cal./mole	19,800 ± 1,000 cal./mole
ΔS^{*}	-25.0 ± 3 e.u.	-18.9 ± 3 e.u.
ΔF^{*}	24,400 ± 900 cal./mole	25,500 ± 1,000 cal./mole

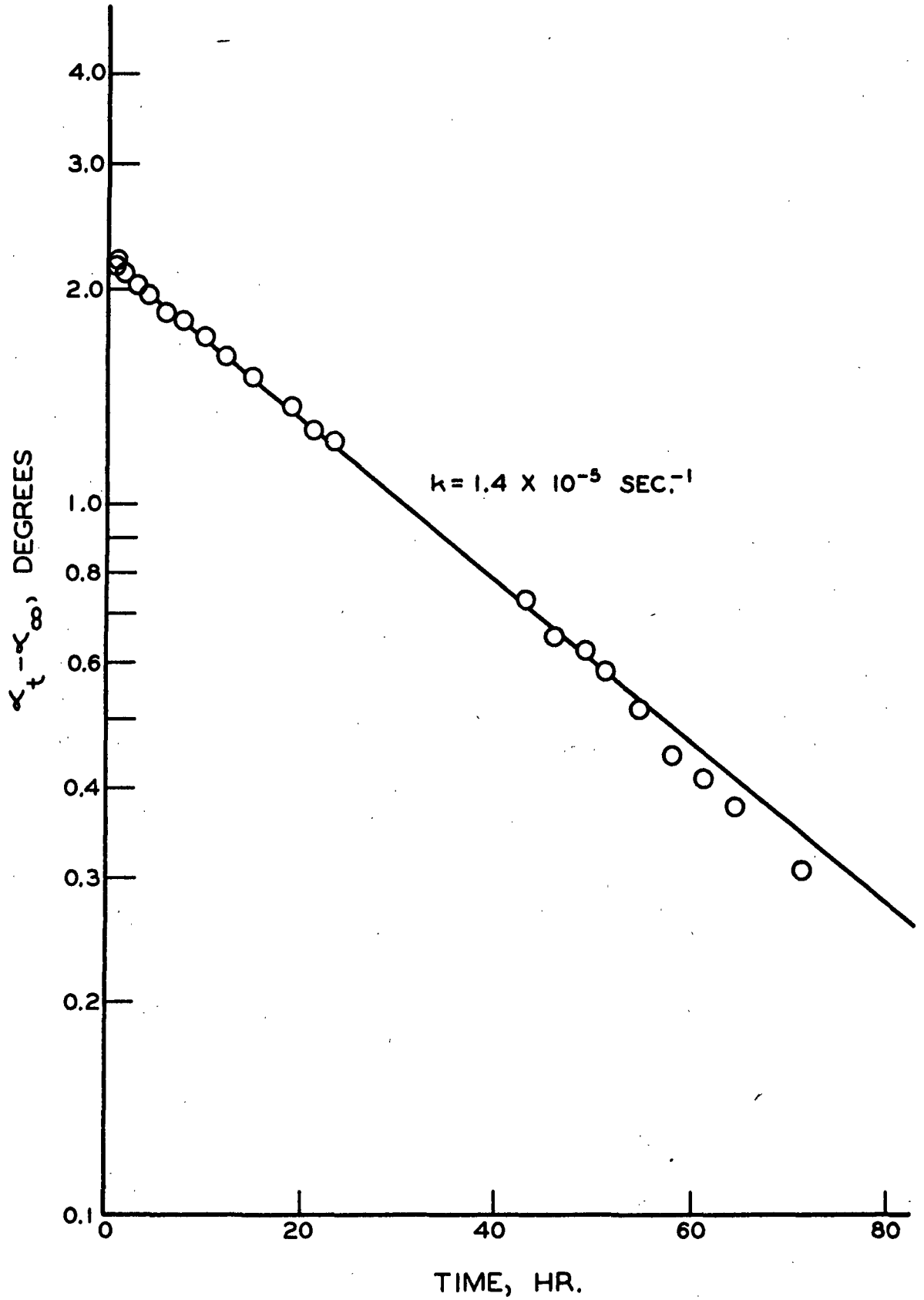


Figure 18. Methanolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide in Methanol:DMF (12:88) at 12.9°C.

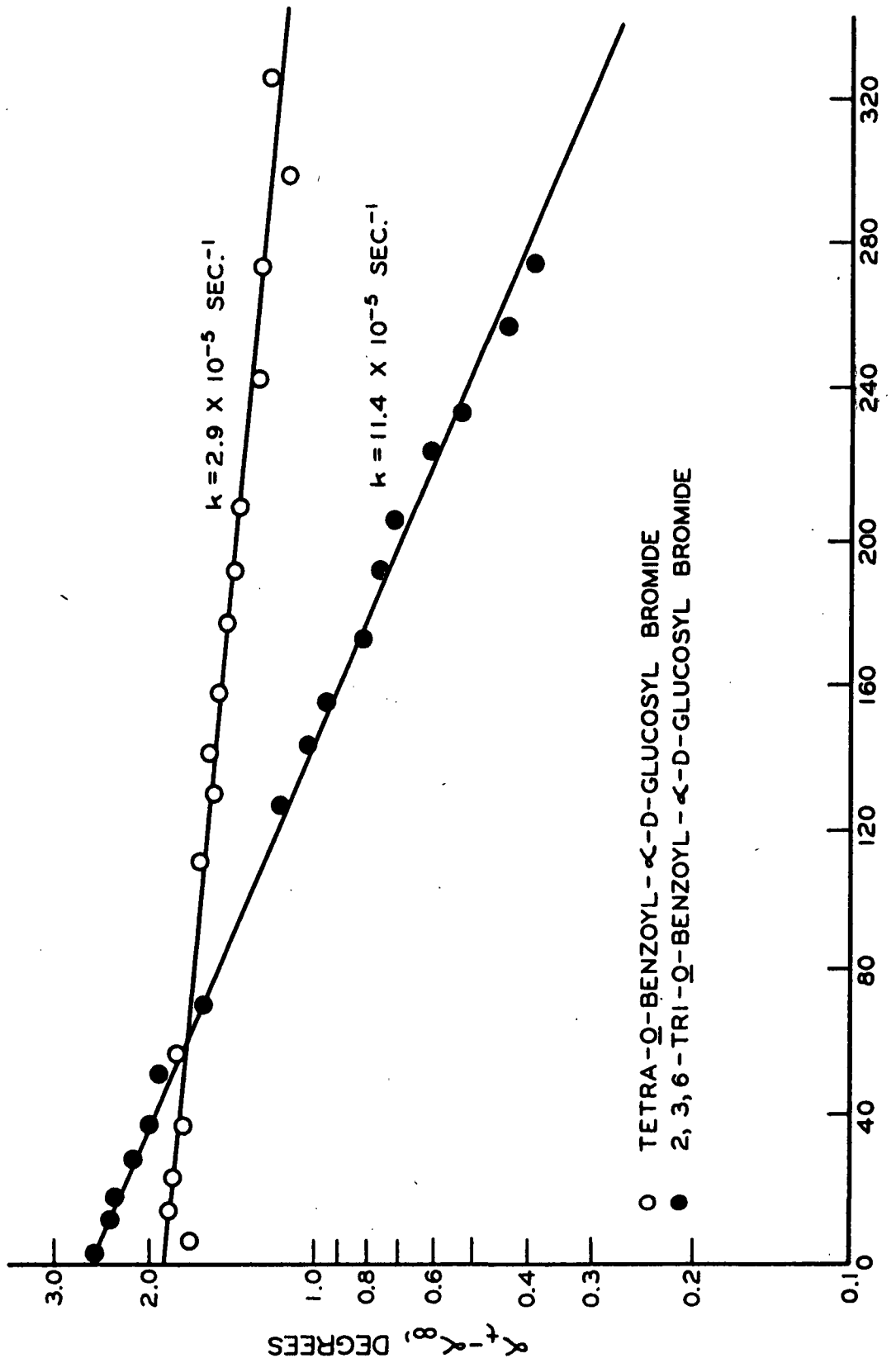


Figure 19. Methanolysis of O-Benzoyl glucosyl halides at 18.5°C. in Methanol:DMF (12:88)

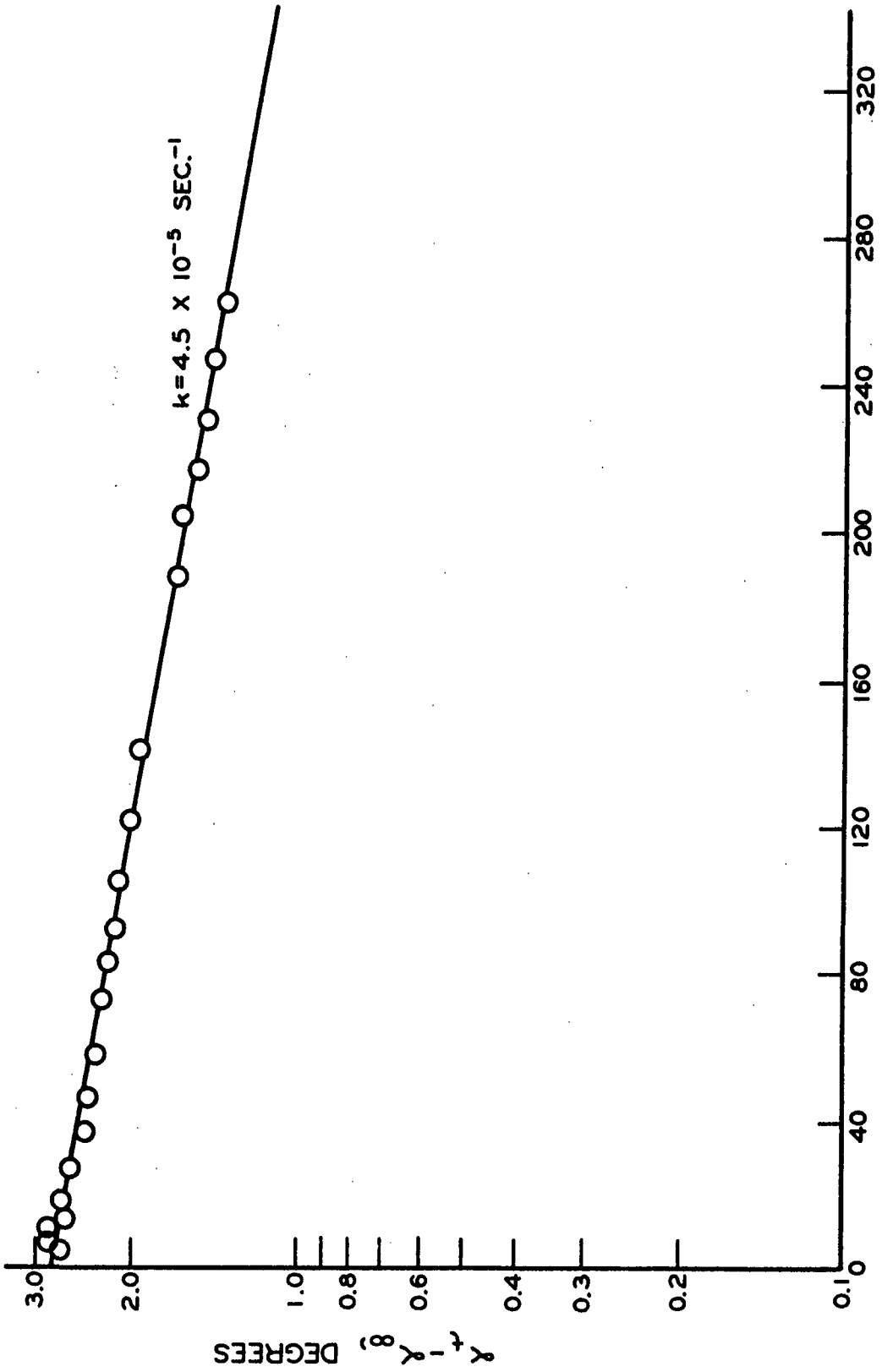


Figure 20. Methanolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide in Methanol:DMF (12:88) at 23.7°C.

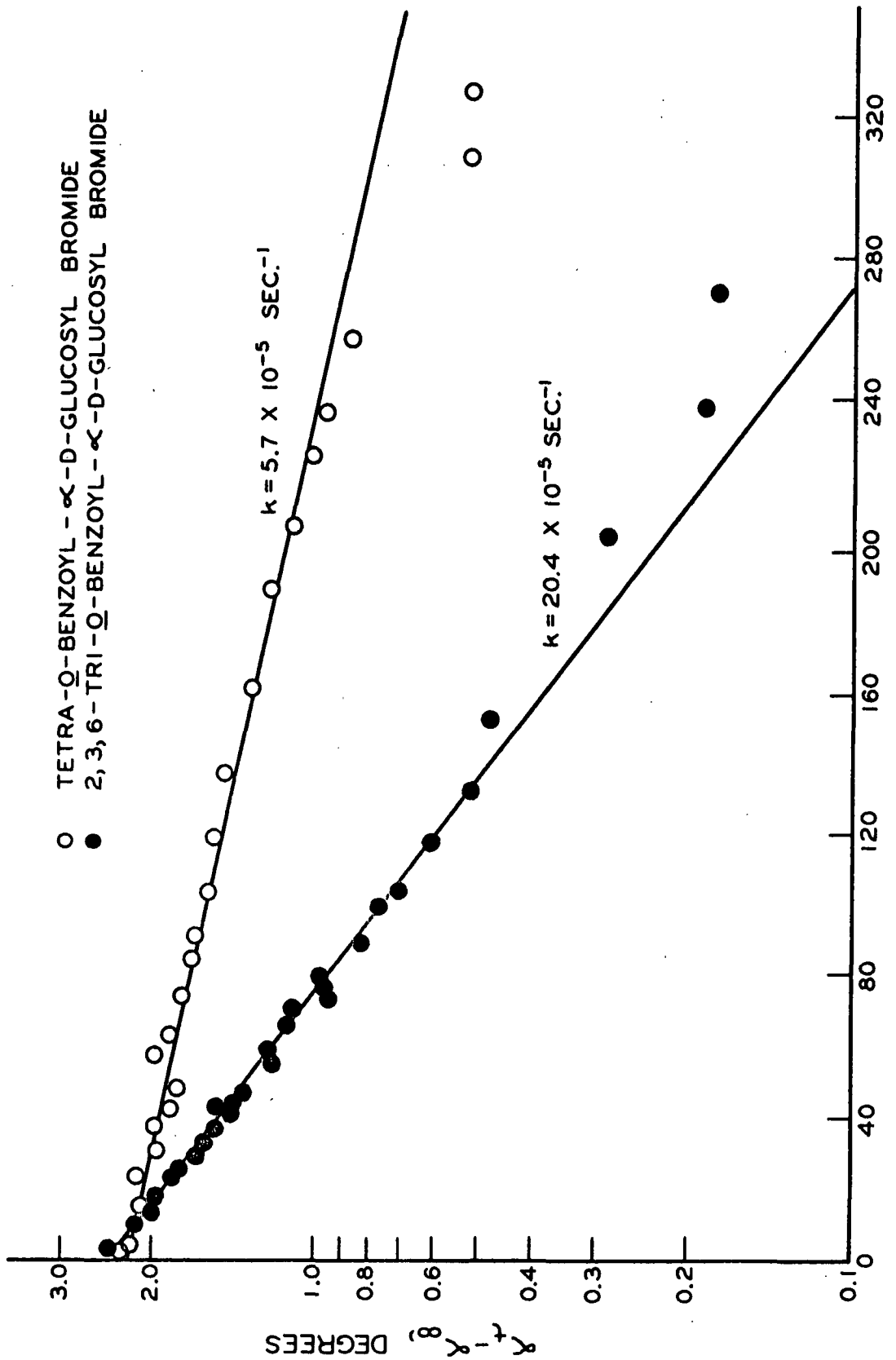


Figure 21. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides at 27.0°C. in Methanol:DMF (12:88)

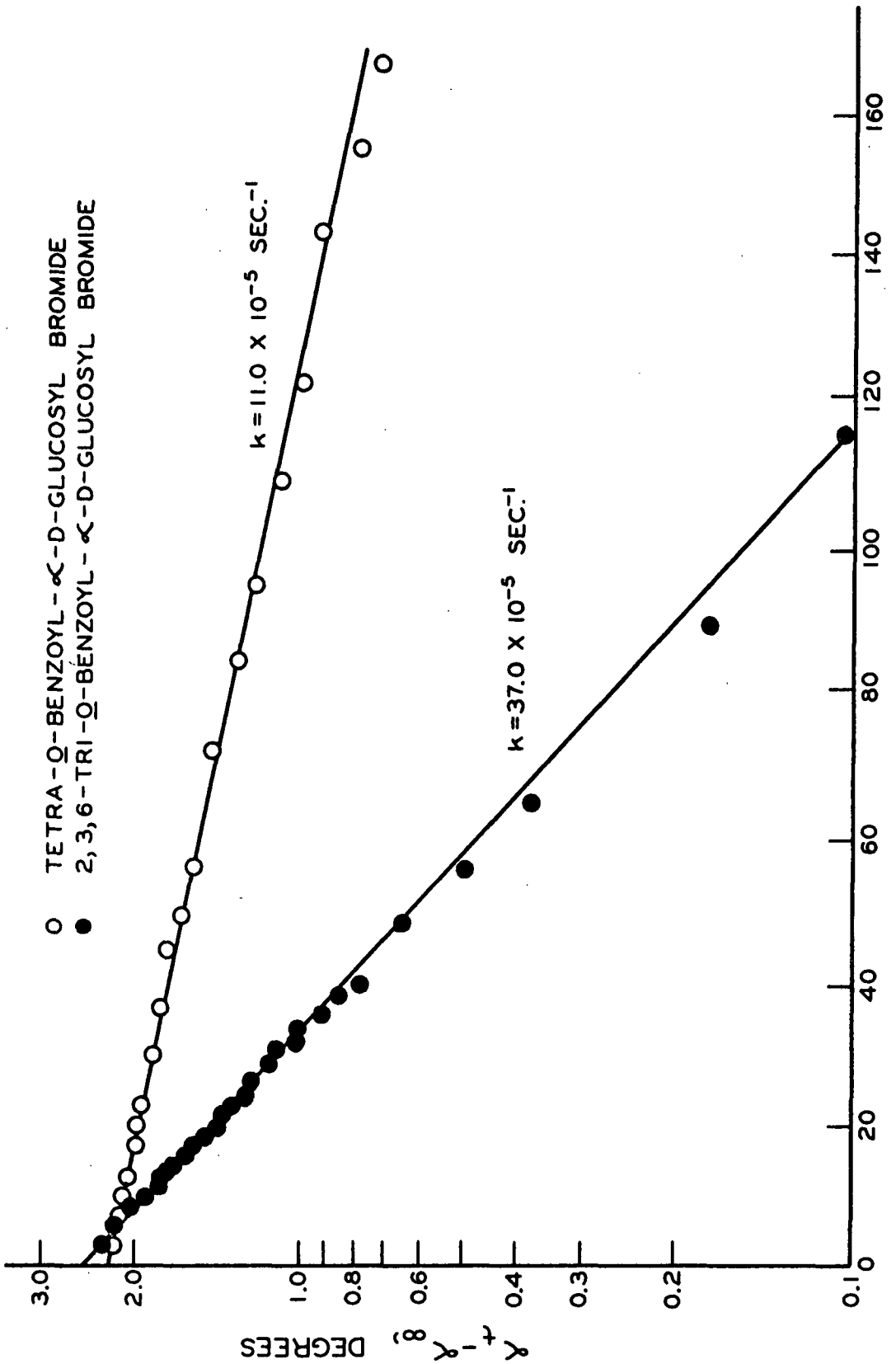


Figure 22. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides in Methanol:DMF (12:88) at 33°C.

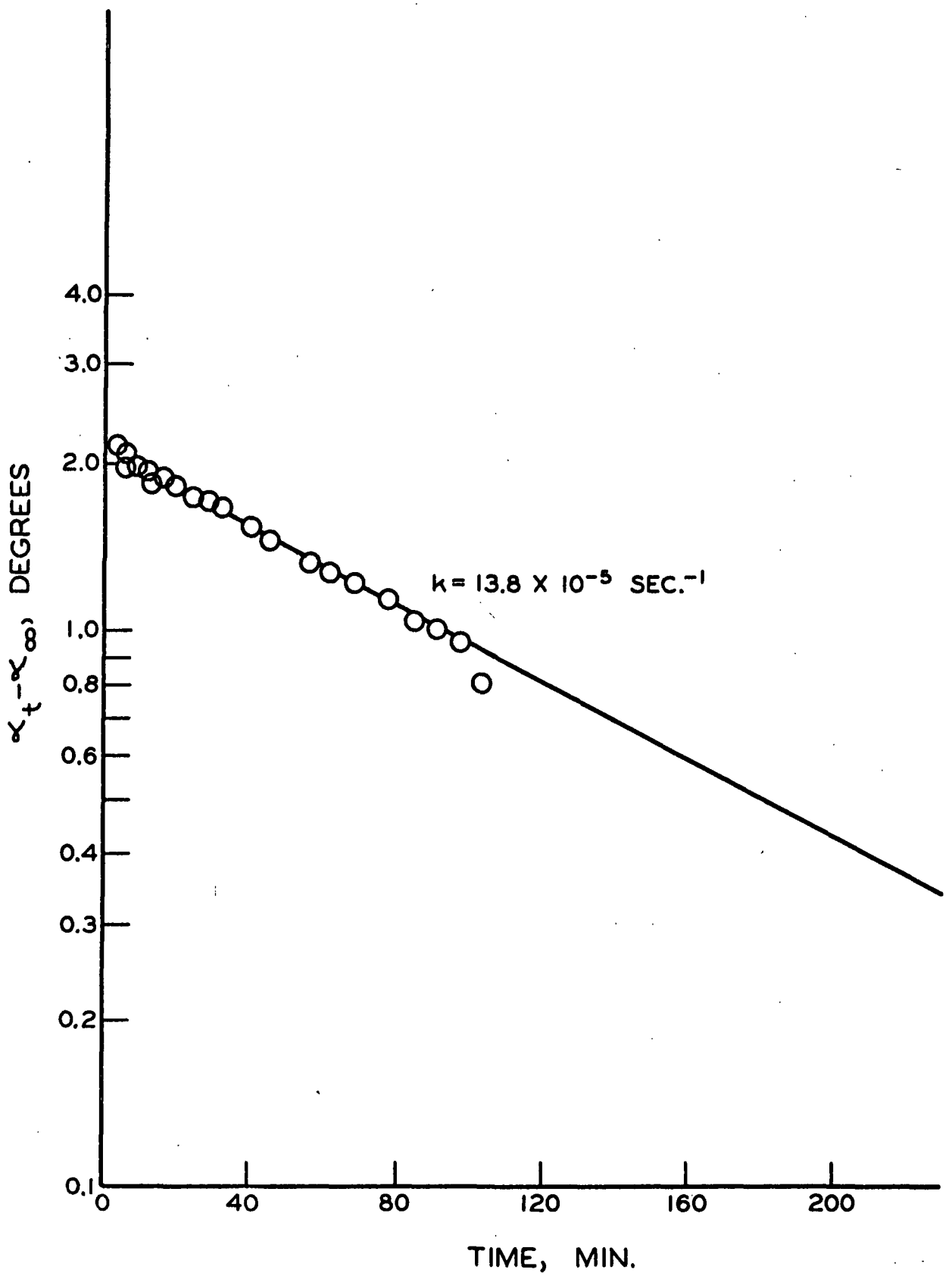


Figure 23. Methanolysis of tetra-O-Benzoyl-α-D-glucosyl Bromide in Methanol:DMF (12:88) at 36.8°C.

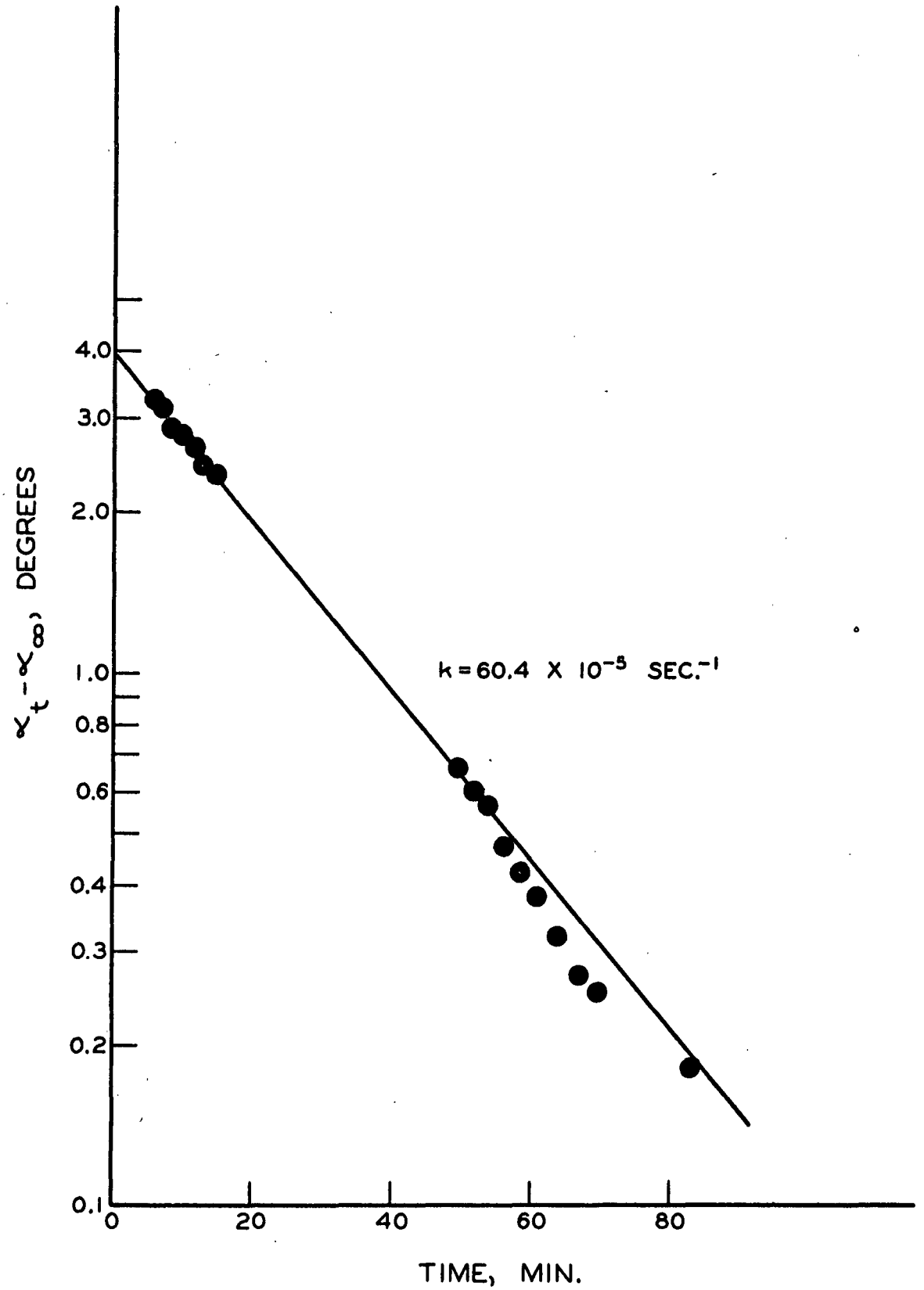


Figure 24. Methanolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide at 37.8°C. in Methanol:DMF (12:88)

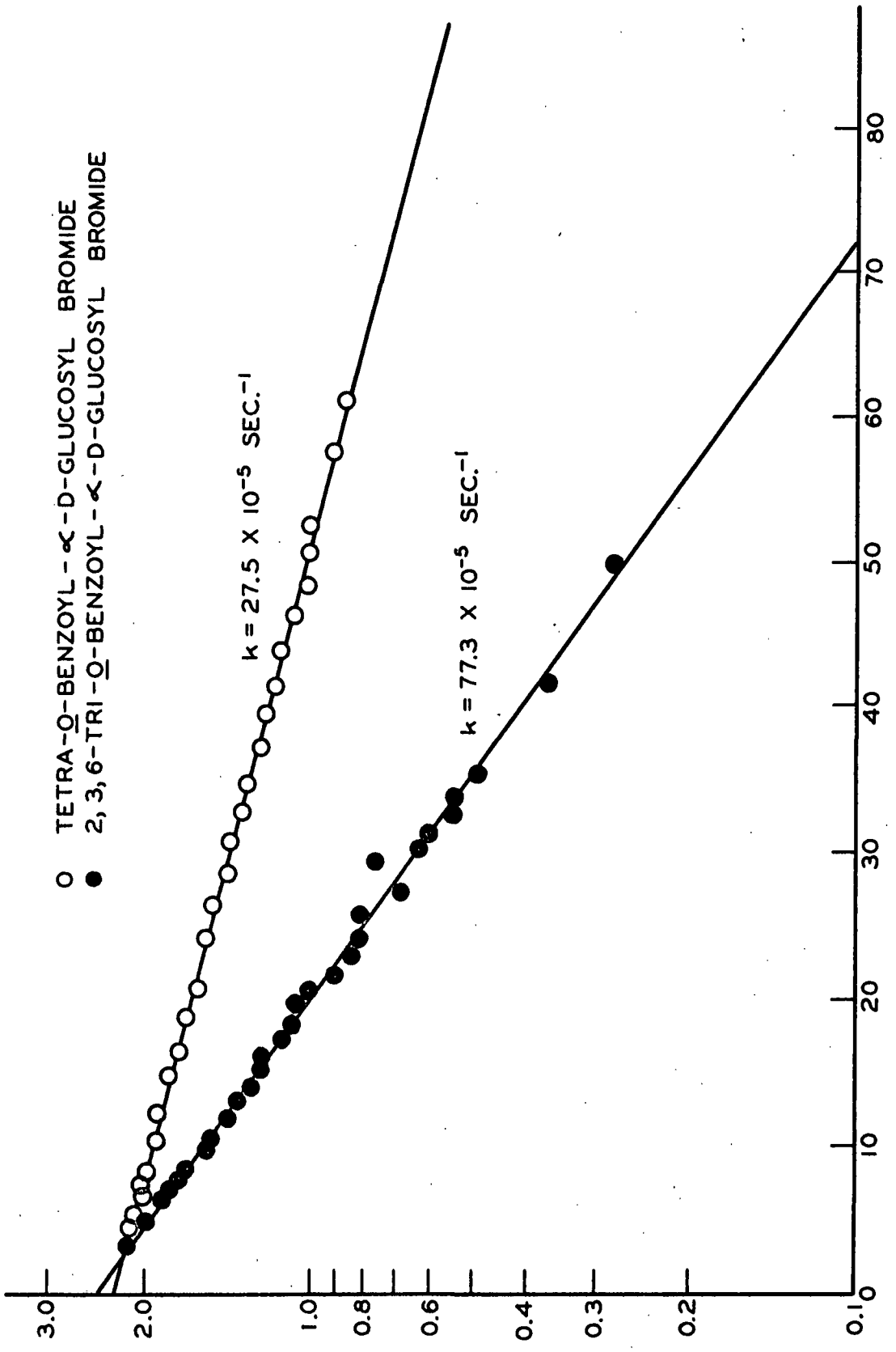


Figure 25. Methanolysis of O-Benzoyl-α-D-glucosyl Bromides at 41.0°C. in Methanol:DMF (12:88)

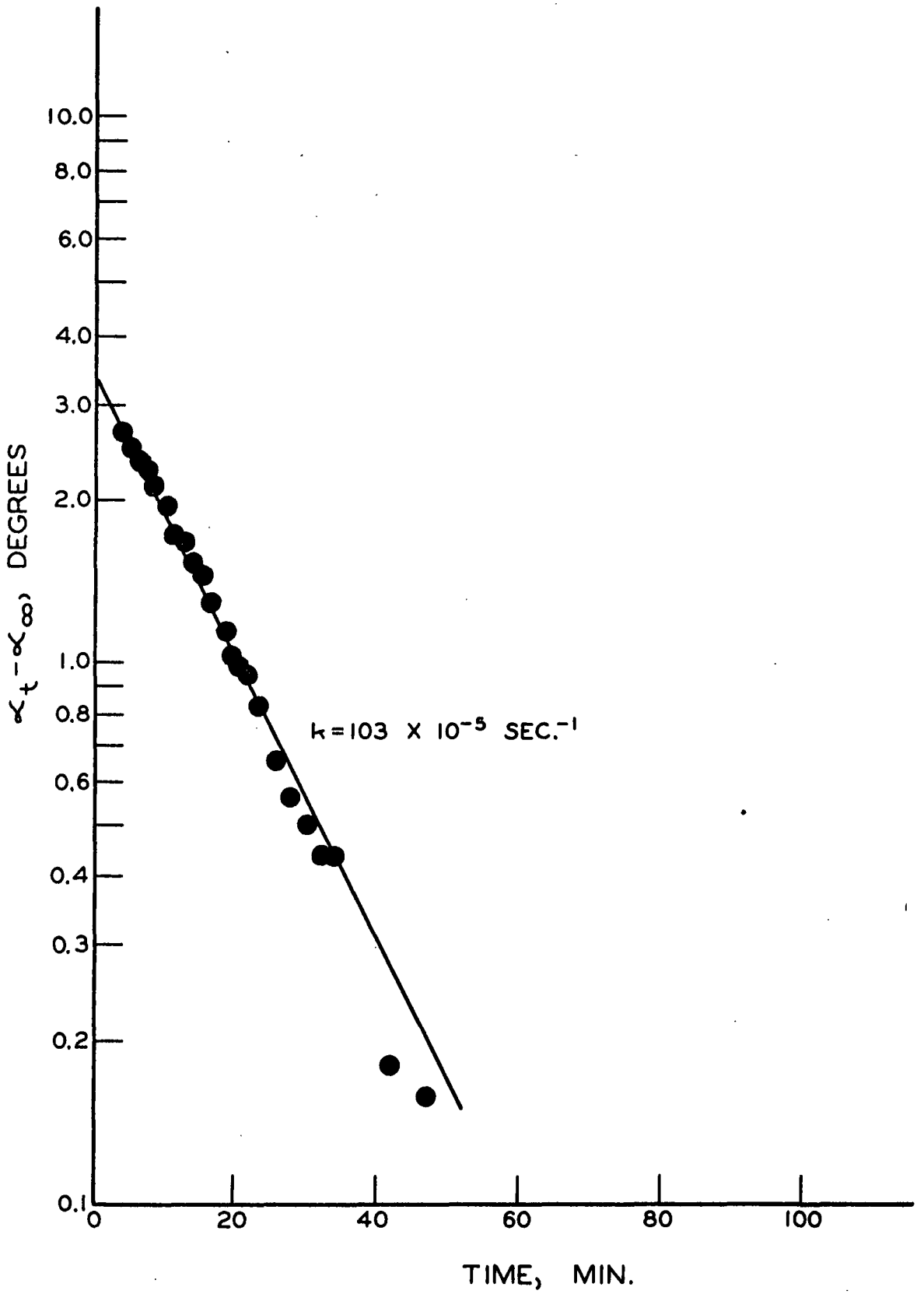


Figure 26. Methanolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide at 46.1°C. in Methanol:DMF (12:88)

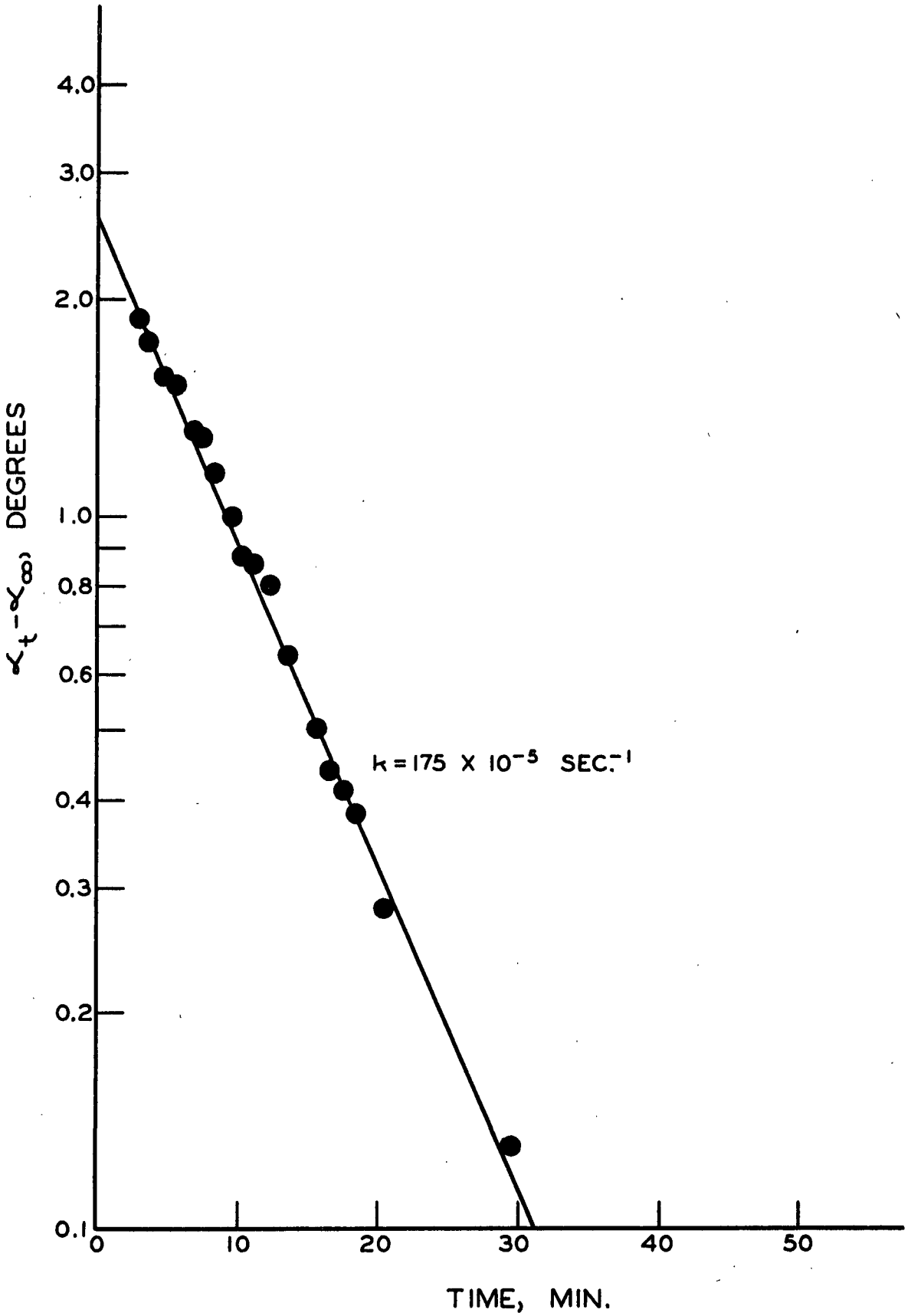


Figure 27. Methanolysis of 2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide at 53.5°C. in Methanol:DMF (12:88)

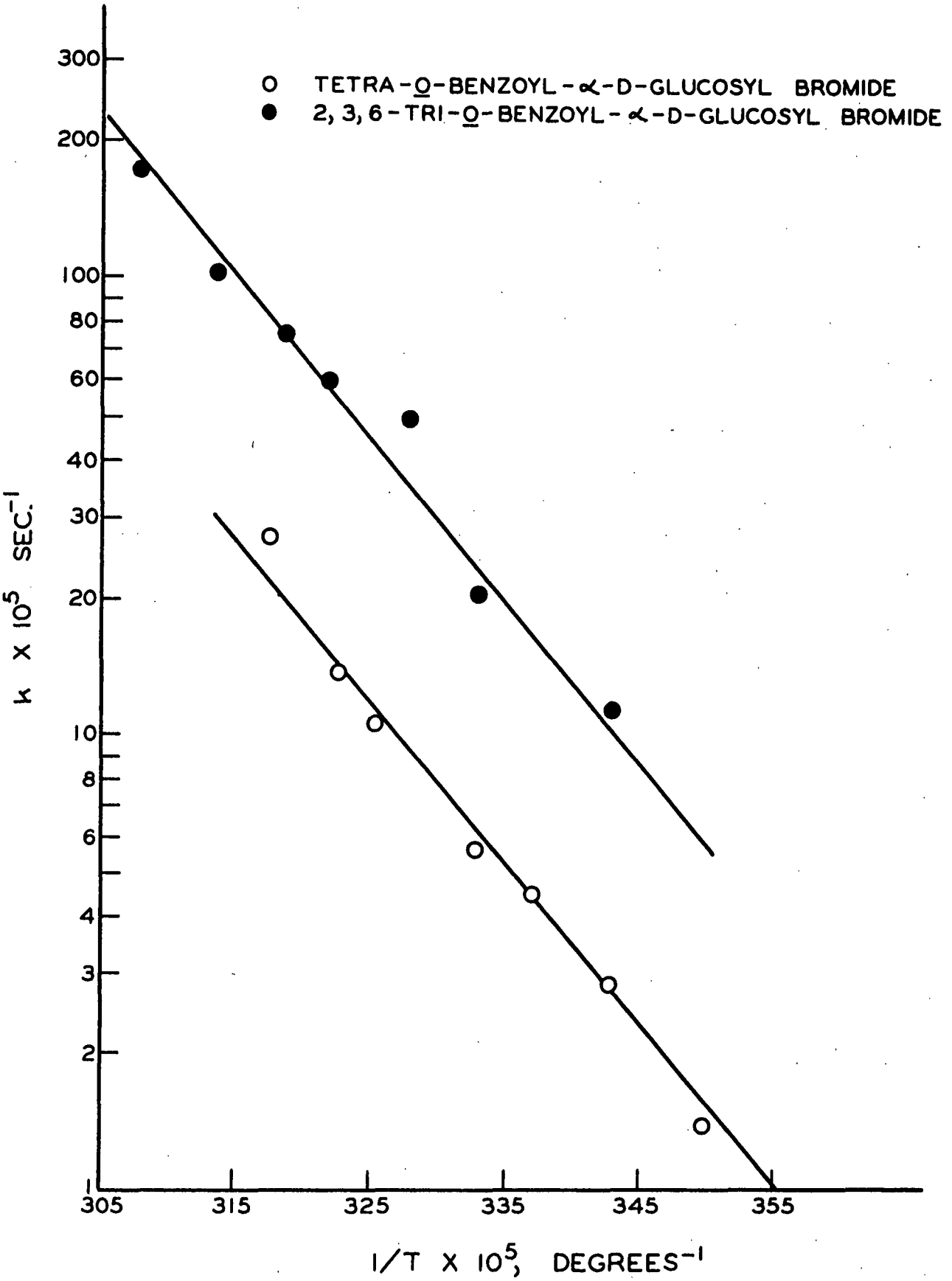


Figure 28. Variation of Rate Constant as a Function of Temperature for Methanolysis of O-Benzoyl-α-D-glucosyl Bromides in Methanol:DMF (12:88)

TABLE VII

ENERGIES OF ACTIVATION IN DIMETHYL FORMAMIDE:METHANOL (88:12)
TEMPERATURE RANGE 13-55°C.

	2,3,6-tri-O-Benzoyl-α-D-glucosyl Bromide	2,3,4,6-tetra-O-Benzoyl-α-D-glucosyl Bromide
E_{exp}	15,300 ± 575 cal./mole	17,280 ± 675 cal./mole
ΔH^{*}	15,900 ± 575 cal./mole	17,980 ± 675 cal./mole
ΔS^{*}	-25.8 ± 1.5 e.u.	-22.1 ± 1.5 e.u.
ΔF^{*}	23,900 ± 575 cal./mole	24,400 ± 675 cal./mole

The rate data definitely show that 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide is more reactive than 2,3,4,6-tetra-O-benzoyl-α-D-glucosyl bromide in methanolysis reactions. Both rates are greatly enhanced by using the more polar solvent dimethyl formamide which is again in agreement with an S_n1 reaction mechanism.

Although serious objections can be raised to the application of the theory of absolute rate processes in calculating activation energies of reactions in solution, the data show a statistically significant difference in the activation energies and entropies of activation for solvolysis reactions in both methanol:dioxane (9:1) and dimethyl formamide: methanol (88:12); however, due to these limitations it is not known whether or not the absolute differences are meaningful. Nevertheless, it should be noted again that the rate data definitely show that 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide is more reactive than 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide, so that it would be expected qualitatively that a finite difference in either activation energy or entropy or both should exist.

Eyring (35) has discussed the effect of substitution in a molecule on activation energy and reactivity. In a reaction of the type

$$X + YZ \longrightarrow X....Y....Z \longrightarrow XY + Z$$

the activation energy depends on four factors:

1. the strength of the bond between Y and Z,
2. the repulsion between X and YZ,
3. the repulsion between XY and Z, and
4. the strength of the bond between X and Y.

As a result of a substitution on a molecule, these four factors that determine activation energy should be altered. Consider the hypothetical case in which a benzoate ester is added to 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide to yield 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromide. It should be possible to neglect inductive effects on the basis that the inductive effect coming from benzoate esters on the C-4 hydroxyl would be superseded by those benzoate esters closer to the active bromide group. Therefore, it is reasonable to assume that the difference in rates of solvolysis of 2,3,6 and 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl bromides cannot be due to factors 1 and 4 above. Thus, the main differences in reactivity can probably be attributed to factors which affect the repulsion between the two halides and methanol. Two such effects would be solvation and steric hindrance.

It would be expected that the free C-4 hydroxyl on 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide would attract methanol to a greater degree than the C-4 benzoate ester on tetra-O-benzoyl-α-D-glucopyranosyl bromide. Thus, a better situation for polarization of the C-Br bond would be sustained.

With respect to steric hindrance, the difference in rate constants is of the same order of magnitude as the difference Newth and Phillips (32) found in the rate of hydrolysis of tetra-O-acetyl glucosyl bromide and tetra-O-acetyl galactosyl bromide. The only difference in these molecules is the configuration of the C-4 acetyl group. The ratio of specific reaction constants k galactose/k glucose is 4.5 to 1. By constructing accurate molecular models of these compounds, Newth and Phillips have shown that the difference in reactivity is related to the degree of crowding about the halide group, and, therefore, the difference in reactivity is due entirely to steric hindrance.

It seems reasonable to assume that qualitatively both solvation and steric hindrance effects contributed to the difference in reactivity of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide and tetra-O-benzoyl-α-D-glucopyranosyl bromide; however, with the data in this present work, it is impossible to quantitatively evaluate the relative importance of each.

EXPERIMENTAL PROCEDURES

SYNTHESIS OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

The following five steps resulted in the synthesis of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide.

PREPARATION OF 4,6-BENZYLIDENE-D-GLUCOPYRANOSE

The 4,6-benzylidene derivative of glucose was prepared by the method of Zervas (36) starting with 130 g. of D-glucose. The glucose, finely powdered, and 100 g. of finely powdered, freshly fused zinc chloride were shaken with 300 ml. of freshly distilled benzaldehyde for 24 hours. The thick liquid was mixed with 400 ml. of ice-cold water. The mixture was filtered and the crystals were washed, first with cold water and then with petroleum ether. This procedure did not prescribe the amount of cold water and petroleum ether required to wash the crude crystals; however, it had been found that a purer product could be obtained by washing with at least 4 liters of each. The crude yield was 33 g.; the melting point, 168°C.; $[\alpha]_D^{23} = +10°$ ($c = 3$, methanol). The crude product could have been purified by recrystallization from hot water made slightly alkaline with ammonia; however, this procedure was not followed.

PREPARATION OF 1,2,3-TRI-O-BENZOYL-4,6-BENZYLIDENE-D-GLUCOPYRANOSE

Thirty-three grams of crude 4,6-benzylidene glucose were dissolved in 99 ml. of anhydrous pyridine, and 59.4 ml. of benzoyl chloride were

added to the solution with cooling. After 30 hours at 25°C., the mixture was poured into 1200 ml. of ice water. The crude product was triturated and filtered off. Recrystallization from ethanol yielded 16.3 g. of pure product melting at 193-194°C., $[\alpha]_D^{25}$ = -10.5° (c = 3, chloroform) (26).

PREPARATION OF 1,2,3-TRI-O-BENZOYL-D-GLUCOPYRANOSE

Sixteen and three-tenths grams of 1,2,3-tri-O-benzoyl-4,6-benzylidene-D-glucopyranose were dissolved in 200 ml. of acetone. Ten milliliters of 2N hydrochloric acid were added to the solution and a temperature of 50°C. was maintained for 2-1/2 hours. The acid was neutralized with barium carbonate; the acetone was filtered off and evaporated to near dryness with the addition of more barium carbonate. Water (500 ml.) was added to the residue, and the water and residue were extracted with chloroform as was the original barium carbonate. The combined chloroform extracts were washed once with water, dried with anhydrous sodium sulfate, and evaporated to a thick sirup. Crystals were obtained from the resulting sirup by dissolving in hot benzene and cooling. Subsequent recrystallizations from benzene resulted in 9 g. of material melting at 108-109°C. (26).

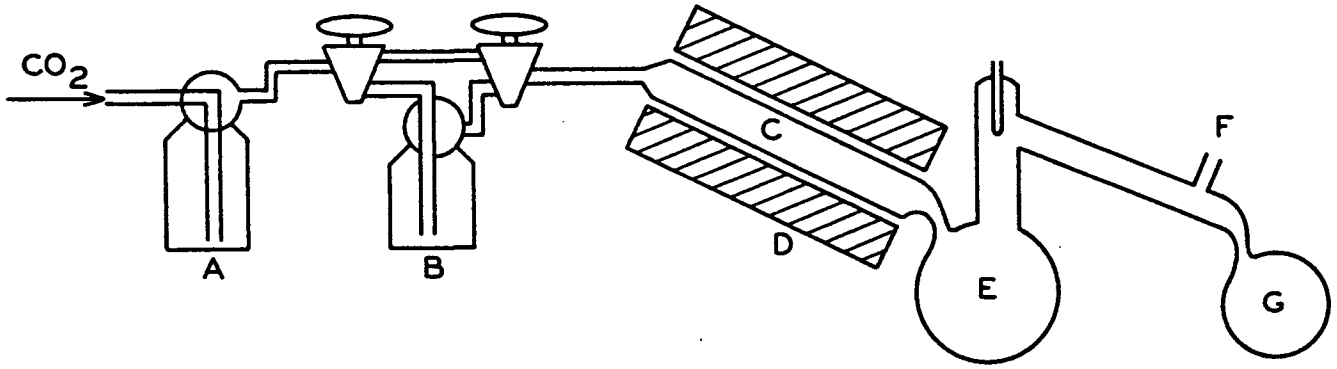
PREPARATION OF 1,2,3,6-TETRA-O-BENZOYL-D-GLUCOSE

Instead of using the previously mentioned method of Brigl and Grüner (26), the following method was patterned after Jermyn (37) who selectively benzoylated the primary C-6 hydroxyl of p-nitrophenyl-2,3-di-O-benzoyl-β-D-glucoside. Eleven grams of 1,2,3-tri-O-benzoyl-D-glucose

were dissolved in 65 ml. of anhydrous pyridine, and 3.5 ml. benzoyl chloride in 20 ml. chloroform were added dropwise with cooling. After 4 hours at 25°C., 4.1 ml. of water were added to the mixture. After one more hour 65 ml. of chloroform and 790 ml. of ice water were added to the reaction mixture. The chloroform was washed once with 700 ml. of ice water and once with 900 ml. of ice cold dilute sulfuric acid. The chloroform layer was dried with anhydrous sodium sulfate and evaporated down to approximately 30 ml. Cooling the chloroform to -5°C. resulted in four grams of almost pure 1,2,3,6-tetra-O-benzoyl-D-glucopyranose with a melting point of 148-150°C. and $[\alpha]_D^{23} = +27°$ (c = 2, chloroform). Nine grams of a less pure product could be obtained by adding petroleum ether (60-110° b.p.) to the mother liquor; the resulting crystals had a melting point of 130-140°C. Recrystallization was from benzene petroleum ether as described by Brigl and Grüner (26).

PREPARATION OF TITANIUM TETRABROMIDE

Since titanium tetrabromide cannot be obtained commercially, it was prepared according to the method prescribed by Young and Fernelius (38). In this method titanium dioxide was heated to 600°C. in the presence of a high-purity carbon. Bromine vapors were then passed over the mixture to form the titanium tetrabromide. The apparatus used in this procedure is shown in Fig. 29. In a typical run the reaction tube "C" was charged with an intimate mixture of 40 g. of titanium oxide and 24 g. of sugar charcoal prepared by burning sucrose at 800°C. (39). Gas washing bottle "A" was filled with concentrated sulfuric acid and bottle



A SULFURIC ACID FOR DRYING OF AIR
B BROMINE
C REACTION CHAMBER
D CYLINDRICAL OVEN
E PRIMARY RECEIVING FLASK
F VENT
G SECONDARY RECEIVING FLASK

Figure 29. Apparatus for the Preparation of Titanium Tetrabromide

"B" was charged with 180 g. of bromine. The furnace was heated to 300°C. and the system was swept with carbon dioxide until it was completely dry. A drying tube filled with Drierite was then attached to point "F". The furnace was heated to 600°C. and the stopcocks were set so that the bromine was swept through the reaction chamber. The titanium tetrabromide was caught in receiving flask "E". After the reaction was completed, the system was swept free of bromine. The titanium tetrabromide was then distilled into receiver "G" keeping only that fraction which boiled near 230°C. The yield was 180 g. For purposes of storing, the titanium tetrabromide was taken up in chloroform.

PREPARATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

Twenty-five one-hundredths of a gram of 1,2,3,6-tetra-O-benzoyl-D-glucopyranose was dissolved in 3 ml. of anhydrous, ethanol-free chloroform to which was added 0.35 ml. of chloroform containing 0.434 g. of titanium tetrabromide per milliliter. After 5 hours of refluxing, 10 ml. of cold acetic acid were added to the dark solution and the chloroform was separated by adding ice-cold water. These steps must be conducted as rapidly as possible so as to avoid hydrolysis of the halide. The chloroform was washed three times with ice water, dried with calcium chloride, and evaporated to dryness in the presence of toluene. The sirup was dissolved in anhydrous ether and small, white, needlelike crystals were obtained by adding pentane and cooling to 0°C. The crystals melted at 148-156°C. and gave a specific optical rotation of +135° (c =

0.4, chloroform). A second recrystallization from anhydrous ether-pentane resulted in crystals with a melting point of 161-163°C. and a specific optical rotation of +181.3° (c = 1, chloroform). Further recrystallizations did not change the physical properties of the crystals. The yield was 48% of the theoretical.

Table VIII is a summary of the yields and physical properties of the intermediates involved in the synthesis of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide.

TABLE VIII

PHYSICAL PROPERTIES OF THE COMPOUNDS INVOLVED IN THE SYNTHESIS OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

	Melting Pt., °C.	Specific Optical Rotation, degrees	Yield, %
4,6-Benzylidene glucose	186-188 (188)[a]	-4.2 (-4.7)[a] Methyl Alcohol	20
4,6-Benzylidene-1,2,3-tri-O-benzoyl-D-glucose	193 (193)	-11 (-10.6) Chloroform	90
1,2,3-tri-O-Benzoyl-D-glucose	108-110 (108)	--	60
1,2,3,6-tetra-O-Benzoyl-D-glucose	153-154 (153-154)	+27 (+27) Chloroform	75
2,3,6-tri-O-Benzoyl-α-D-glucopyranosyl bromide	161-163	+181.3 Chloroform	48

[a] The figures in parentheses refer to the values given in the literature.

PREPARATION OF METHYL 2,3,6-TRI-O-BENZOYL-β-D-GLUCOPYRANOSIDE

Methyl 2,3,6-tri-O-benzoyl-β-D-glucopyranoside was prepared in the following manner as a step in the identification of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide. A solution of 15 ml. of chloroform and 30 ml. of methanol was used to dissolve 0.48 g. of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide. To this solution was added 0.17 g. of freshly prepared silver oxide. The mixture was shaken for 2 days, after which the solids were filtered off and washed with chloroform. The filtrate was evaporated to a sirup which was crystallized from ether-pentane to yield 0.28 g. of white crystalline material melting at 142-144°C. and showing a specific optical rotation of +77.2° (c = 1, chloroform). Further recrystallization from ether-pentane gave crystals melting at 143.5-144.5°C. and showing a specific optical rotation of +81.2°C. (c = 1, chloroform).

METHODS USED IN ATTEMPTED POLYCONDENSATION OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE

PURIFICATION OF SOLVENTS

The four solvents used in the polycondensation reactions were purified as described below:

Chloroform

U.S.P. chloroform (500 ml.) was shaken with 500 ml. of 12% sulfuric acid for one hour on a mechanical shaker. The chloroform layer was separated, neutralized with a saturated solution of sodium bicarbonate

and washed well with water. It was then shaken one hour with 100 g. of calcium chloride, filtered and distilled. After drying a short time over phosphorus pentoxide, the chloroform was redistilled and stored over Drierite (19).

Pyridine

Pyridine (500 ml.) was distilled through a 40-cm. Vigreux column over barium oxide and was stored over barium oxide.

Dimethyl Formamide

The dimethyl formamide was shaken with solid potassium hydroxide, separated and fractionally distilled through a 40-cm. Vigreux column (40).

Nitromethane

Nitromethane was dried over phosphorus pentoxide and then fractionally distilled through a 40-cm. Vigreux column (41).

PREPARATION OF ACID ACCEPTORS

Silver oxide and the mercuric salts used as the acid acceptors in the polycondensation reactions were obtained as follows:

Silver Oxide

Thirty-six grams of sodium hydroxide pellets were added portionwise, with constant stirring, to 500 ml. of water which initially had a

temperature of 60°C. Thirty-two and one-half grams of potassium peroxydisulfate in the form of an aqueous slurry were added to the alkaline solution whose temperature was 85°C.; this was followed by the addition of 51 g. of silver nitrate dissolved in a minimum amount of water. The temperature of the resulting mixture was raised to 90°C., and stirring was continued for approximately 15 minutes.

The precipitate of black silver oxide was filtered on a large Büchner funnel, and the sulfate ions were removed by washing with water which had been made slightly alkaline with sodium hydroxide. The product was air-dried overnight and finally dried in a vacuum oven maintained at 50°C. for 2 hours. The yield was 17.4 g. (93%) (48).

Mercuric Salts

Commercial reagent-grade mercuric acetate and cyanide salts were used in all cases. The mercuric salts were dried by heating in a vacuum oven for 2 hours at 50°C. and then stored in a desiccator.

PROCEDURE FOR CONDUCTING REACTIONS

Ten-centimeter lengths of 15-mm. pyrex tubing were sealed at one end, cleaned thoroughly and dried in an oven maintained at 120°C. The tubes were then fitted at the open end with a drying tube. A typical reaction in which silver oxide was used as the acid acceptor is described below: Silver oxide (0.2000 g.) was put into the glass tube followed by 0.6800 g. of Drierite. (The Drierite had been preheated at 240°C. for 2-2.5 hours and then cooled over phosphorus pentoxide.)

One milliliter of the appropriate solvent was placed in the tube and the mixture was put on a mechanical shaker for 30 minutes. The 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide (0.2500 g.) was dissolved in a minimum of the appropriate solvent with gentle warming and added to the previous mixture. Iodine (0.0500 g.) was also added to the mixture. The tube was then sealed air-tight in an oxygen torch flame. The tube was agitated in a constant temperature bath maintained within ±0.3°C. of the desired temperature. At the end of the reaction period, the tube was broken open and the solids were filtered off through a coarse, fritted glass microfilter. Sodium thiosulfate was used to neutralize the iodine and the solution was evaporated to 0.5 ml. Nine milliliters of barium methoxide and 9 ml. of methanol were added to the solution in order to debenzoylate the products. This solution was allowed to stand at 0°C. overnight. A phenolphthalein test was made for excess barium methoxide; and if no excess was present, the above debenzoylation process was repeated. The solution was concentrated to 0.5 ml. and spotted on paper chromatograms which had already been spotted with glucose and the cellodextrin series of sugars. The chromatograms were developed in ethyl acetate:pyridine:water (8:2:1) and sprayed with p-anisidine hydrochloride reagent.

When mercuric salts were used as acid acceptors, the following amounts of reagents were used: 0.0461 g. of mercuric cyanide and 0.1015 g. of 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide. The debenzoylation and chromatography processes for mercuric salts were similar to those described above for silver oxide, except that the chromatograms were also spotted with known maltodextrins.

SOLVOLYSIS REACTIONS

PURIFICATION OF SOLVENTS

Dimethyl Formamide

Dimethyl formamide was purified as previously described (page 74).

Dioxane

Dioxane was purified by refluxing over sodium pellets for 18 hours. The dioxane was then fractionally distilled through a 40-cm. Vigreux column and stored over sodium.

Methanol

Iodine (0.5 g.) and magnesium (5.0 g.) were placed in a 2-l. flask with 50-75 ml. of methanol. The flask was gently warmed until the iodine disappeared. An additional 900 ml. of methanol was then added to the flask and the contents were refluxed for one-half hour. The mixture was distilled with the exclusion of moisture and fractionally redistilled from sulfanilic acid (42).

Ethanol

Commercial absolute ethanol was refluxed over calcium oxide for 5 hours and then fractionally distilled through a 60-cm. Vigreux column (43).

Water

Equilibrium water was used in all solvolysis reactions in which water was required.

PREPARATION OF TETRA-O-BENZOYL-α-D-GLUCOPYRANOSYL BROMIDE (44)

The preparation of α-D-glucose pentabenzoate, an intermediate, required for the synthesis of tetra-O-benzoyl-α-D-glucopyranosyl bromide is described below:

Preparation of α-D-Glucopyranose Pentabenzoate (45)

Alpha-D-glucopyranose pentabenzoate was prepared according to the method described in C440 National Bureau of Standards (46) in 98% yield giving a product melting at 186.5-187°C. and an $[\alpha]_D^{22}$ +137.8° (c = 2, chloroform). The method employed benzoyl chloride in the presence of dry pyridine.

Preparation of Tetra-O-benzoyl-α-D-glucopyranosyl Bromide

The method of Ness, Fletcher, and Hudson (44) was used to prepare tetra-O-benzoyl-α-D-glucopyranosyl bromide. In this method the α-D-glucopyranose pentabenzoate was dissolved in ethylene dichloride and treated with hydrogen bromide in glacial acetic acid. The product (90% yield) melted at 129-131°C. and had an $[\alpha]_D^{23}$ +123.1° (c = 2, chloroform).

PREPARATION OF TETRA-O-ACETYL-α-D-GLUCOPYRANOSYL BROMIDE

This compound was prepared according to the method of Fischer (49) in which penta-O-acetyl-β-D-glucose was dissolved in glacial acetic acid saturated with hydrogen bromide. The product melted at 89-90°C. and had a $[\alpha]_D^{22}$ +195.3° (c = 2, chloroform).

PROCEDURES FOR CONDUCTING SOLVOLYSIS REACTIONS

Approximately 0.2000-0.3000 g. (0.02-0.06M) of the appropriate halide was weighed into a 10-ml. volumetric flask, and the flask was stoppered and put into a constant temperature bath for 30 minutes. All solvents to be used in the reaction were also stored in this bath which was maintained at the temperature at which the reaction was to be run. The first solvent to be added to the flask was always the nonreactive solvent. The stopwatch was started after half of the reactive solvent had been added. As quickly as possible the solution was transferred to a water-jacketed polarimeter tube and optical rotation readings were begun. Temperature readings throughout the reaction were taken in the constant temperature bath which was used to pump constant temperature water through the jacketed-polarimeter tube. This bath was maintained usually within $\pm$0.05°C. of the desired temperature. After the optical rotation had reached an equilibrium value, the temperature of the reaction itself was obtained. This temperature was found never to be more than 1°C. different than the bath temperature. The reaction temperature was always used in calculating activation energies.

SUMMARY AND CONCLUSIONS

A survey of the literature has shown that the Koenigs-Knorr reaction has wide applicability in the synthesis of simple glycosides and disaccharides. Recently, Haq and Whelan have shown that this applicability can be extended to the synthesis of the gentiodextrin series of sugars by means of a single polycondensation reaction. Using 2,3,4-tri-O-acetyl-α-D-glucopyranosyl bromide as a monomer, Haq and Whelan were able to produce the gentiodextrins with a maximum D.P. of nine and a maximum in the weight distribution curve at a D.P. of three.

The purpose of this dissertation was to study the applicability of the Koenigs-Knorr reaction to the synthesis of the cellodextrin series of oligosaccharides. Since the monomer required for this polycondensation reaction was a new compound, it was also desirable to characterize its reactivity by means of solvolysis reactions.

It was found possible to synthesize the desired monomer, 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide, by brominating 1,2,3,6-tetra-O-benzoyl-α-D-glucopyranose with titanium tetrabromide.

Eleven attempts were made to polycondense this material varying acid acceptors, solvent, and temperature of reaction. The results of these condensations showed that under the best conditions only cellobiose (β, 1→4 linkage) and maltobiose, and maltotriose could be obtained (α, 1→4 linkage). It should be noted that these products were only tentatively identified by paper chromatography.

Since the monomer was a bifunctional glucose molecule containing a C-1 bromide group and a C-4 hydroxyl group, the failure to undergo appreciable polycondensation must have been due to a relatively low reactivity of one or both of these groups. Recent reports in the literature have indeed shown that the C-4 hydroxyl is much less reactive than the C-6 hydroxyl. Also, it has long been an accepted fact that benzoate esters decrease the reactivity of a glucosyl halide due to steric hindrance. Based on these two facts, it would be expected that this attempt to synthesize the cellodextrins would be less productive than the synthesis of the gentiodextrins conducted by Haq and Whelan. Nevertheless, an experimental program was enacted to quantitatively evaluate the extent to which the bromide group was at fault.

This experimental program involved a comparison of the reactivity by solvolysis reactions in identical solvents of tetra-O-acetyl-α-D-glucopyranosyl bromide, tetra-O-benzoyl-α-D-glucopyranosyl bromide, and 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide. Before this comparison could be made, it had to be demonstrated that both O-benzoyl and O-acetyl glucosyl bromides would undergo methanolysis by the same reaction mechanism.

Newth and Phillips have studied the mechanism of solvolysis of O-acetyl-glucosyl bromides and have concluded that the mechanism is S_n1 (unimolecular nucleophilic substitution) where the rate-controlling step is the ionization or polarization of the C-1 halogen bond. In this dissertation a study was made of the rate of solvolysis of the two benzoate-substituted halides as a function of Lewis base strength. This

study presented good evidence that the rate of solvolysis was independent of Lewis base strength. Therefore, it could be concluded that the two benzoate-substituted glucosyl bromides studied underwent solvolysis also by the S_n1 mechanism. It was thus considered legitimate to compare the reactivities of the O-acetate and O-benzoate substituted glucosyl bromides by means of solvolysis reactions.

The rates of methanolysis in methanol:dioxane (9:1) fell in the order of 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide > tetra-O-benzoyl-α-D-glucosyl bromide > tetra-O-acetyl-α-D-glucosyl bromide. Although no data are available on the reactivity of 2,3,4-tri-O-acetyl-α-D-glucosyl bromide, it would be expected, based on the above data, that its reactivity would be greater than tetra-O-acetyl-α-D-glucosyl bromide and less than 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide.

Although these solvolysis measurements were made only in a single solvent system, it was still possible to conclude that the O-acetate- and O-benzoate-substituted glucosyl bromides are of the same order of reactivity. From this assumption, it was concluded that the lack of polycondensation of 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide as compared with 2,3,4-tri-O-acetyl-α-D-glucosyl bromide was due entirely to the difference in reactivity of the C-4 and C-6 hydroxyl groups.

In the final phase of this dissertation, a comparison was made between the reactivity of 2,3,6-tri-O-benzoyl-α-D-glucopyranosyl bromide and tetra-O-benzoyl-α-D-glucopyranosyl bromide, as a means of assessing the importance of the C-4 benzoate ester on reactivity of the halide.

These data show that the 2,3,6-tri-O-benzoyl-α-D-glucosyl bromide definitely has the higher rate constant at a given temperature. The differences in rate constants were shown to be due to statistically different activation energies and entropies; however, due to limitations in applying the theory of absolute rates to reactions in solutions, it was impossible to designate any meaning to these differences.

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APPENDIX I

CALCULATION OF SPECIFIC RATE CONSTANTS BY MEANS OF POLARIMETRY

Since a solvolysis reaction is a first-order reaction and since the solvolysis of O-benzoyl-α-D-glucopyranosyl bromides has been shown to be unimolecular, it is possible to write the rate equation as follows:

$$dc/dt = k[c] \qquad (1)$$

where c = the concentration of the halide at time t.

The integrated form of this equation is

$$\ln c_o/c = kt \qquad (2)$$

where c = the concentration of the halide at time t,

c_o = the concentration of the halide at time t equals zero,

t = the time in seconds, and

k = the specific rate constant.

However, $c_o = c + c_{ROH}$ (3)

where c_{ROH} = the concentration of glycoside at any time.

Therefore, since $\alpha = a\,[\alpha] / c$ (4)

where α = the observed optical rotation,

$[\alpha]$ = the specific optical rotation

a = a constant

it is possible to say that

$$\alpha_t = c_t[\alpha]_{RBr} + c_{ROH}[\alpha]_{ROH} \qquad (5)$$

$$= c_t[\alpha]_{RBr} + (c_o - c_t)[\alpha]_{ROH} \qquad (6)$$

where α_t = the observed rotation of the solution of glucosyl halide and glucoside at time t. Therefore,

$$\alpha_t = c_t\left\{[\alpha]_{RBr} - [\alpha]_{ROH}\right\} + c_o[\alpha]_{ROH} \tag{7}$$

and $$c_t = \alpha_t - c_o[\alpha]_{ROH}/[\alpha]_{RBr} - [\alpha]_{ROH} \tag{8}$$

Since $$[\alpha]_{ROH} = \alpha_\infty/c_o \tag{9}$$

where α_∞ = the final equilibrium rotation, assuming the reaction goes to completion, and

$$[\alpha]_{RBr} = \alpha_o/c_o$$

Therefore, $$c_t = (\alpha_t-\alpha_\infty)/(\alpha_o/c_o - \alpha_\infty/c_o) = c_o(\alpha_t - \alpha_\infty)/(\alpha_o - \alpha_\infty) \tag{10}$$

and $$\ln c_o/c_o(\alpha_t - \alpha_\infty)/(\alpha_o - \alpha_\infty) = kt \tag{11}$$

Therefore, $$\ln(\alpha_o - \alpha_\infty)/(\alpha_t - \alpha_\infty) = kt \tag{12}$$

or $$\ln(\alpha_t - \alpha_\infty)/(\alpha_o - \alpha_\infty) = -kt \tag{13}$$

According to Equation (13) a plot of $\ln(\alpha_t - \alpha_\infty)$ *versus* time should give a straight line whose slope is $-k$, the specific rate constant. Applying this equation to the data in this thesis involves the assumption that the presence of two optically active species in solution does not alter the specific optical rotation of either. The method of least squares was used to compute the rate constants from the data. It was found that the error on the limits on the slope of the plot of $\ln \alpha_t - \alpha_\infty$ *versus* time was approximately 10% and the correlation coefficients on these plots were usually better than 0.99. The rate constants for hydrolysis were calculated by estimating $d\alpha_t/dt$ at $t = 0$ since mutarotation prohibits applying the above-described method for the calculation of rate constants. In all cases the initial slopes were taken for determining rate constants.

APPENDIX II

DATA FOR CALCULATION OF RATE CONSTANTS

The following appendix contains the original data from which the rate constants reported in this thesis were calculated. In this appendix α_t is the observed optical rotation at the given time for a specific reaction.

TABLE IX

HYDROLYSIS OF TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN WATER:DMF (12:88)

Temperature: 33.4°C.

Concn. = 0.1970 g./10 ml.

Time, min.	α_t
3.1	6.17
5.5	5.82
7.7	5.54
9.5	5.43
11.8	5.07
14.3	4.81
21.1	4.26
23.2	4.28
25.3	4.05
27.6	4.07
35.6	3.83
39.2	3.85
42.8	3.65
46.6	3.67
49.7	3.65
54.0	3.60
59.6	3.59
79.6	3.55
98.3	3.55

α_∞ = 3.55

TABLE X

HYDROLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN WATER:DMF (12:88)

Temperature: 33.4°C.

Concn. = 0.3873 g./25 ml.

Time, min.	α_t
1.3	3.97
7.0	3.89
11.5	3.73
14.5	3.64
17.6	3.49
20.5	3.45
22.9	3.41
25.7	3.33
29.1	3.23
32.5	3.17
36.2	3.09
39.8	3.00
43.6	2.94
46.8	2.88
53.0	2.75
71.3	2.69
79.6	2.43
89.3	2.32
104.2	2.18
110.2	2.13
121.8	2.06
146.2	1.95
181.7	1.88
199.5	1.85
215.8	1.86
249.0	1.82
297.0	1.84

$\alpha_\infty = 1.81$

TABLE XI

ETHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN ETHANOL:DMF (2:8)

Temperature: 33.5°C.

Concn. = 0.1582 g./10 ml.

Time, min.	α_t
1.0	3.95
4.3	4.02
6.9	4.00
7.5	3.98
10.7	3.94
16.5	3.89
40.8	3.60
44.0	3.54
48.2	3.53
52.7	3.47
68.7	3.36
73.8	3.27
79.2	3.26
84.1	3.19
94.6	3.10
102.6	3.07
121.8	2.94
160.4	2.66
175.1	2.61
188.9	2.53
204.9	2.50
240.0	2.34
267.8	2.20
332.4	2.01
601.5	1.72
624.0	1.69

$\alpha_\infty = 1.74$

TABLE XII

ETHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN ETHANOL:DMF (2:8)

Temperature: 33.4°C.

Concn. = 0.1927 g./10 ml.

Time, min.	α_t
4.8	6.56
6.2	6.60
9.5	6.32
11.5	6.30
15.0	6.12
17.8	5.99
20.4	5.91
23.4	5.72
27.3	5.61
31.0	5.50
34.2	5.41
37.5	5.26
40.7	5.20
44.4	5.07
50.3	4.91
66.8	4.51
76.7	4.30
84.6	4.18
101.2	4.00
107.3	3.94
116.4	3.88
139.9	3.70
178.2	3.68
197.0	3.61
212.8	3.63
246.5	3.62

$\alpha_\infty = 3.62$

TABLE XIII

METHANOLYSIS OF 2,3,4,6-TETRA-O-ACETYL-α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

Temperature: 36.9°C.

Concn. = 0.1363 g./10 ml.

Time, min.	α_t
2.6	4.39
3.8	4.42
4.8	4.32
5.5	4.29
6.0	4.31
7.0	4.27
8.1	4.27
9.9	4.30
11.8	4.30
14.7	4.27
18.5	4.25
26.2	4.26
35.9	4.27
55.0	4.22
79.3	4.10
91.9	4.10
180.0	3.91
206.8	3.81
234.3	3.76
326.5	3.53
394.2	3.36
503.0	3.04
577.2	2.87
644.0	2.64
716.7	2.52
1382.5	1.18
1408.0	1.17
1449.0	1.10
1497.0	1.06
1682.0	0.87
1707.0	0.82
1750.0	0.83
1936.0	0.65
2626.0	0.30

α_∞ = 0.02

Temperature: 42.5°C.

Concn. not taken, but range from 0.12 to 0.18 g./10 ml.

Time, min.	α_t
3.0	7.47
4.3	7.54
7.3	7.49
10.6	7.40
25.1	7.37
41.6	7.21
66.3	6.97
74.4	6.88
82.6	6.80
90.0	6.74
98.1	6.66
142.1	6.20
157.6	6.07
169.9	5.94
185.8	5.72
201.6	5.54
229.3	5.24
244.2	5.11
257.8	4.96
289.8	4.62
309.8	4.38
329.0	4.17
346.0	4.03
417.7	3.33
490.3	2.76
520.8	2.54
548.8	2.37
677.2	1.69
1376.0	0.42

α_∞ = 0.17

TABLE XIV

METHANOLYSIS OF 2,3,4,6-TETRA-O-ACETYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

Temperature: 51.0°C.

Concn. = 0.1782 g./10 ml.

Time, min.	α_t
3.1	6.42
3.7	6.70
5.3	6.57
7.7	6.58
9.7	6.54
17.9	6.46
26.8	6.27
34.0	6.13
38.8	6.05
46.3	5.92
52.3	5.80
61.3	5.70
67.8	5.54
76.8	5.37
84.5	5.21
90.8	5.08
138.0	4.21
148.8	4.00
160.2	3.79
160.8	3.66
172.8	3.56
197.7	3.15
208.3	3.00
237.4	2.55
265.3	2.17
281.9	2.01
318.6	1.63
366.6	1.31
490.0	0.67
568.7	0.52
660.7	0.30

α_∞ = 0.02

Temperature: 60.0°C.

Concn. = 0.1789 g./10 ml.

Time, min.	α_t
4.1	6.58
5.7	6.48
6.8	6.50
12.3	6.31
22.0	5.88
23.4	5.86
26.3	5.75
29.5	5.63
34.0	5.43
36.9	5.38
39.7	5.24
42.8	5.11
48.5	4.89
52.2	4.77
57.2	4.54
61.7	4.39
69.0	4.15
76.0	3.84
82.5	3.64
85.7	3.55
89.7	3.40
93.5	3.24
98.1	3.15
102.5	3.02
107.0	2.90
111.3	2.72
115.7	2.65
184.0	1.29
245.0	0.72
389.9	0.17
596.5	-0.01

α_∞ = -0.01

TABLE XV

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL-DIOXANE (9:1)

Temperature: 13.0°C.

Concn. = 0.1206 g./10 ml.

Time, hr.	α_t
.1	3.80
.2	3.80
.4	3.82
.6	3.82
.7	3.81
.8	3.79
1.0	3.76
1.2	3.76
2.2	3.75
2.7	3.73
3.9	3.69
4.7	3.67
5.3	3.66
6.5	3.60
8.1	3.56
9.7	3.54
10.9	3.48
12.2	3.45
22.1	3.22
23.7	3.19
24.9	3.15
25.9	3.17
27.6	3.06
28.9	3.04
30.9	2.96
32.7	2.93
35.9	2.83
46.8	2.57
49.2	2.51
51.9	2.50
53.6	2.52
71.8	2.04
73.7	2.09
82.0	1.97
94.9	1.82
120.7	1.62
129.4	1.45
142.2	1.38

α_∞ = 1.38

Temperature: 27.1°C.

Concn. = 0.3345 g./25 ml.

Time, hr.	α_t
.1	6.09
.3	5.88
1.2	5.17
2.2	4.42
2.5	4.12
2.9	3.84
3.5	3.98
3.9	3.70
4.9	3.56
5.5	3.17
6.1	3.05
7.1	2.86
7.9	2.64
10.2	2.50
11.3	2.33
12.1	2.31

α_∞ = 2.16

TABLE XVI

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

Temperature: 35.2°C.

Concn. = 0.2946 g./25 ml.

Time, hr.	α_t
.05	4.25
.08	4.22
.1	4.26
.2	4.18
.3	4.06
.4	3.83
.8	3.42
.9	3.30
1.1	3.14
1.4	2.91
1.6	2.88
1.7	2.69
1.9	2.56
2.6	2.20
2.9	2.13
3.2	2.10
3.6	2.03
3.8	1.98
4.7	1.95
5.5	1.78
6.0	1.80
6.3	1.77
7.1	1.71
7.9	1.73
8.7	1.75
9.5	1.72
9.9	1.72
11.9	1.70
13.5	1.70
17.8	1.68
22.9	1.69
24.2	1.66
25.2	1.67
28.2	1.67
29.5	1.67
35.5	1.70
47.6	1.68

α_∞ = 1.67

Temperature: 41.5°C.

Concn. = 0.2914 g./25 ml.

Time, min.	α_t
3.6	4.30
12.4	3.81
14.3	3.79
17.3	3.66
19.7	3.61
21.3	3.52
23.0	3.49
24.9	3.44
28.2	3.27
30.4	3.25
32.9	3.26
35.2	3.18
40.2	3.10
50.2	2.79
54.1	2.70
58.5	2.64
62.2	2.56
69.9	2.46
76.3	2.46
94.9	2.22
100.1	2.16
110.9	2.10
123.4	1.97
133.5	1.88
148.9	1.87
155.8	1.75
169.8	1.81
188.8	1.75
202.2	1.70
222.4	1.63
242.8	1.63
258.3	1.63
288.3	1.62
309.5	1.72
326.5	1.59
344.3	1.59
362.3	1.57
400.0	1.55

α_∞ = 1.55

TABLE XVII

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

Temperature: 18.1°C.

Concn. = 0.3133 g./25 ml.

Time, hr.	α_t
.3	3.46
.7	3.41
1.1	3.46
2.1	3.42
4.2	3.37
5.6	3.33
7.3	3.27
10.8	3.15
13.1	3.06
23.4	2.76
26.7	2.67
30.5	2.53
32.4	2.48
34.5	2.41
36.6	2.35
47.4	2.13
50.5	2.14
54.5	2.03
57.5	2.04
60.4	2.01
71.6	1.83
74.9	1.82
78.4	1.78
83.4	1.59
95.9	1.49
100.8	1.45
122.5	1.29
143.8	1.15

α_∞ = 1.05

Temperature: 27.1°C.

Concn. = 0.3743 g./25 ml.

Time, hr.	α_t
.1	4.29
.6	4.19
1.0	4.12
2.0	3.95
2.8	3.86
3.3	3.84
3.7	3.76
4.2	3.67
4.7	3.67
5.2	3.55
6.3	3.49
6.9	3.44
7.8	3.34
8.7	3.23
10.9	3.05
12.1	3.00
12.9	2.97

α_∞ = 1.19

TABLE XVIII

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

Temperature: 35.2°C.

Concn. = 0.4033 g./25 ml.

Time, hr.	α_t
.05	4.57
.1	4.55
.4	4.48
.5	4.46
.7	4.40
1.6	4.10
2.4	3.93
2.9	3.74
3.1	3.69
3.9	3.50
4.9	3.29
5.6	3.12
6.0	3.06
6.4	2.95
6.9	2.86
7.5	2.73
8.8	2.55
10.4	2.26
14.7	1.84
19.8	1.57
21.2	1.45
22.2	1.43
25.3	1.31
26.8	1.31
32.7	1.23
44.8	1.22

α_∞ = 1.21

Temperature: 41.5°C.

Concn. = 0.3788 g./25 ml.

Time, min.	α_t
3.6	4.24
5.6	4.28
8.6	4.22
11.4	4.19
14.6	4.18
16.0	4.15
17.9	4.13
21.9	4.13
23.4	4.10
26.5	4.07
31.5	4.07
41.7	3.99
47.3	3.95
51.4	3.89
55.3	3.89
62.4	3.75
69.1	3.81
81.9	3.67
92.9	3.62
104.1	3.57
116.4	3.46
126.7	3.40
139.3	3.28
153.9	3.20
162.7	3.16
182.0	3.01
195.3	2.96
218.0	2.76
235.9	2.63
251.5	2.57
271.7	2.43
301.8	2.45
319.6	2.38
338.1	2.31
355.8	2.28
392.9	2.12
404.9	2.11
483.6	1.92
518.2	1.82
598.0	1.69
650.0	1.50
791.9	1.37

α_∞ = 1.20

TABLE XIX

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 12.9°C.

Concn. = 0.1345 g./10 ml.

Time, hr.	α_t
.07	3.65
.08	3.61
.1	3.60
.2	3.55
.3	3.57
.7	3.53
1.7	3.43
2.2	3.39
3.4	3.27
4.2	3.23
4.8	3.14
6.0	3.03
7.7	2.93
9.2	2.79
10.4	2.69
11.7	2.64
21.8	2.15
23.2	2.08
24.1	2.05
25.5	2.01
27.4	1.94
28.5	1.87
30.3	1.84
32.2	1.80
35.5	1.73
46.4	1.57
48.7	1.56
51.5	1.49
53.1	1.52
71.3	1.42
73.2	1.43
81.5	1.40
94.4	1.41

α_∞ = 1.41

Temperature: 18.3°C.

Concn. = 0.3137 g./25 ml.

Time, min.	α_t
7.0	3.60
14.8	3.76
24.0	3.72
38.1	3.65
58.0	3.68
111.8	3.52
130.0	3.42
140.9	3.45
159.1	3.40
176.7	3.33
190.5	3.29
209.4	3.26
244.7	3.16
275.1	3.13
300.0	2.99
327.0	3.10
349.4	2.95
413.4	2.82
485.1	2.70
512.6	2.69
617.1	2.50
764.0	2.31
1339.8	1.88

α_∞ = 1.88

TABLE XIX

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 12.9°C.

Concn. = 0.1345 g./10 ml.

Time, hr.	α_t
.07	3.65
.08	3.61
.1	3.60
.2	3.55
.3	3.57
.7	3.53
1.7	3.43
2.2	3.39
3.4	3.27
4.2	3.23
4.8	3.14
6.0	3.03
7.7	2.93
9.2	2.79
10.4	2.69
11.7	2.64
21.8	2.15
23.2	2.08
24.1	2.05
25.5	2.01
27.4	1.94
28.5	1.87
30.3	1.84
32.2	1.80
35.5	1.73
46.4	1.57
48.7	1.56
51.5	1.49
53.1	1.52
71.3	1.42
73.2	1.43
81.5	1.40
94.4	1.41

α_∞ = 1.41

Temperature: 18.3°C.

Concn. = 0.3137 g./25 ml.

Time, min.	α_t
7.0	3.60
14.8	3.76
24.0	3.72
38.1	3.65
58.0	3.68
111.8	3.52
130.0	3.42
140.9	3.45
159.1	3.40
176.7	3.33
190.5	3.29
209.4	3.26
244.7	3.16
275.1	3.13
300.0	2.99
327.0	3.10
349.4	2.95
413.4	2.82
485.1	2.70
512.6	2.69
617.1	2.50
764.0	2.31
1339.8	1.88

α_∞ = 1.88

TABLE XX

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 18.4°C.

Concn. = 0.3447 g./25 ml.

Time, min.	α_t
3.2	5.50
12.8	5.33
18.8	5.27
29.8	5.11
39.2	4.99
53.2	4.88
72.8	4.54
126.8	4.11
144.3	3.95
155.6	3.88
173.5	3.74
191.9	3.69
205.4	3.64
224.3	3.53
235.1	3.46
259.7	3.37
275.5	3.32
290.5	3.30
314.5	3.25
331.2	3.15
362.0	3.13
427.9	3.03
498.8	3.00
537.8	2.95

α_∞ = 2.93

Temperature: 27.4°C.

Concn. = 0.3371 g./25 ml.

Time, min.	α_t
2.7	5.52
4.3	5.40
5.8	5.39
10.7	5.24
13.8	5.14
17.9	5.04
21.7	4.93
25.2	4.86
29.0	4.74
32.2	4.70
37.0	4.59
40.3	4.50
42.2	4.50
44.2	4.48
47.2	4.41
51.2	4.36
55.6	4.25
59.7	4.27
65.8	4.16
69.8	4.14
73.9	4.00
75.5	4.00
79.8	4.00
89.0	3.86
97.4	3.79
104.3	3.73
117.1	3.63
132.1	3.54
150.8	3.50
202.1	3.31
220.5	3.30
239.1	3.21
272.1	3.20
325.9	3.05

α_∞ = 3.02

TABLE XXI

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 23.7°C.

Concn. = 0.3217 g./25 ml.

Time, min.	α_t
4.9	4.57
7.1	4.62
10.4	4.63
13.4	4.45
18.0	4.41
26.9	4.37
36.6	4.26
45.7	4.22
57.5	4.16
72.8	4.07
83.2	4.01
92.8	3.96
105.5	3.90
120.9	3.83
130.7	3.74
188.5	3.48
205.3	3.43
216.9	3.30
230.8	3.27
247.5	3.20
262.3	3.14
279.1	3.10
349.0	2.87
402.5	2.70
487.7	2.50
646.3	2.23
1345.7	1.81
1380.8	1.81

α_∞ = 1.78

Temperature: 27.3°C.

Concn. = 0.3414 g./25 ml.

Time, min.	α_t
4.4	4.08
7.8	4.07
14.8	4.00
22.9	4.04
30.0	3.87
36.9	3.85
42.4	3.73
48.1	3.66
56.9	3.85
62.5	3.74
74.0	3.64
83.8	3.58
90.5	3.55
103.0	3.45
118.2	3.42
137.0	3.35
160.4	3.18
188.2	3.06
206.4	2.97
225.0	2.88
237.7	2.82
257.9	2.70
309.1	2.36
327.0	2.35
422.0	2.29
512.7	2.17
504.8	2.09
632.0	1.99
750.8	1.83

α_∞ = 1.83

TABLE XXII

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 33.0°C.

Concn. = 0.1438 g./10 ml.

Time, min.	α_t
4.2	3.64
6.7	3.62
9.6	3.57
12.5	3.54
16.9	3.48
19.7	3.49
22.4	3.45
29.5	3.36
35.0	3.28
42.1	3.22
48.6	3.13
55.2	3.06
71.3	2.93
83.8	2.78
94.9	2.69
108.9	2.53
122.0	2.44
143.1	2.37
154.9	2.22
166.6	2.16
177.4	2.07
187.1	2.04
196.6	1.95
207.6	1.92
242.4	1.80
268.3	1.71
288.3	1.68
303.9	1.62
322.4	1.60
348.7	1.55
417.0	1.51
517.8	1.42

α_∞ = 1.40

Temperature: 36.9°C.

Concn. = 0.1286 g./10 ml.

Time, min.	α_t
3.3	3.45
4.4	3.29
5.5	3.26
6.5	3.34
8.2	3.25
10.2	3.22
12.3	3.15
15.6	3.17
18.6	3.11
23.7	3.00
27.8	2.98
31.4	2.96
39.3	2.81
44.2	2.75
55.8	2.60
61.3	2.56
67.9	2.51
77.4	2.42
84.3	2.32
90.0	2.30
96.7	2.25
102.0	2.19
107.9	2.13
113.5	2.10
118.8	2.06
124.6	2.04
129.6	2.02
183.2	1.73
207.9	1.66
225.0	1.54
243.2	1.52
281.0	1.46
324.0	1.39
358.1	1.36
401.4	1.28
495.9	1.28
572.0	1.28

α_∞ = 1.28

TABLE XXIII

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 32.0°C.

Concn. = 0.1210 g./10 ml.

Time, min.	α_t
4.1	5.30
6.1	5.18
8.4	5.01
9.9	4.90
11.2	4.78
12.1	4.75
13.3	4.72
14.4	4.64
15.5	4.60
17.0	4.52
18.2	4.45
19.4	4.40
21.0	4.34
22.5	4.29
24.1	4.21
25.8	4.20
28.5	4.08
29.8	4.06
31.6	3.97
33.0	3.97
35.4	3.85
37.5	3.79
39.8	3.71
47.9	3.57
55.2	3.42
64.9	3.28
89.8	3.09
116.6	3.01
113.1	2.95
148.0	2.91

α_∞ = 2.91

Temperature: 37.8°C.

Concn. = 0.1960 g./10 ml.

Time, min.	α_t
5.7	6.83
6.7	6.68
8.0	6.43
9.5	6.33
11.1	6.19
12.9	6.01
14.4	5.92
49.5	4.22
51.5	4.16
53.7	4.13
55.9	4.03
58.3	3.98
60.5	3.94
63.7	3.88
66.5	3.83
69.4	3.81
74.8	3.79
83.4	3.74
339.3	3.56

α_∞ = 3.56

TABLE XXIV

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 41.5°C.

Concn. = 0.1391 g./10 ml.

Time, min.	α_t	Time, min. (Cont'd)	α_t (Cont'd)
2.8	4.96	36.8	3.03
3.8	4.76	38.5	3.01
5.3	4.63	40.4	2.98
6.7	4.45	42.0	2.92
7.2	4.38	47.1	2.90
7.9	4.32	50.8	2.83
8.9	4.26	66.9	2.77
9.9	4.13	68.7	2.76
10.4	4.12	70.4	2.70
11.2	4.11	72.6	2.70
12.0	3.98	75.3	2.63
13.1	3.92	77.6	2.58
14.2	3.88	79.9	2.58
15.4	3.79	84.5	2.58
16.2	3.79	88.6	2.60
17.8	3.68	101.3	2.57
18.8	3.64	110.3	2.57
19.9	3.62	120.1	2.57
21.2	3.56	123.3	2.57
22.1	3.46	196.0	2.56
23.2	3.40		
24.6	3.37		α_∞ = 2.55
25.9	3.37		
27.5	3.24		
29.2	3.26		
30.6	3.19		
31.7	3.15		
32.9	3.10		
34.3	3.10		
35.5	3.04		

TABLE XXV

METHANOLYSIS OF TETRA-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 42.0°C.

Concn. = 0.1448 g./10 ml.

Time, min.	α_t	Time, min. (Cont'd)	α_t (Cont'd)
3.9	3.57	87.8	1.93
4.7	3.56	93.6	1.89
5.5	3.52	95.9	1.90
6.9	3.41	98.9	1.84
7.8	3.42	101.7	1.83
8.7	3.43	105.5	1.79
10.7	3.36	109.3	1.79
12.7	3.33	115.4	1.76
15.0	3.24	123.9	1.72
16.8	3.17	144.5	1.60
19.0	3.10	158.1	1.59
21.0	3.01	184.2	1.48
23.2	3.00	199.3	1.47
24.3	2.98	345.8	1.39
26.6	2.94		
28.8	2.84	α_∞ =	1.39
30.9	2.83		
32.9	2.75		
35.0	2.71		
37.5	2.65		
39.7	2.60		
41.8	2.58		
43.9	2.53		
46.3	2.48		
48.5	2.40		
50.9	2.42		
52.7	2.40		
57.7	2.30		
60.9	2.25		
84.5	2.01		

TABLE XXVI

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-
α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

Temperature: 46.1°C.

Concn. = 0.1960 g./10 ml.

Time, min.	α_t
4.7	5.70
5.4	5.53
6.7	5.41
7.7	5.38
8.8	5.20
10.2	4.99
11.2	4.80
12.5	4.75
14.0	4.60
15.3	4.52
16.6	4.38
18.1	4.22
19.4	4.11
20.5	4.07
21.7	4.04
23.0	3.91
25.0	3.74
27.3	3.64
30.0	3.58
33.7	3.47
42.2	3.26
47.3	3.24
83.7	3.08

$\alpha_\infty = 3.08$

Temperature: 54.0°C.

Concn. = 0.3556 g./25 ml.

Time, min.	α_t
3.1	3.99
3.9	3.76
4.6	3.67
5.7	3.64
6.8	3.41
7.4	3.38
8.3	3.25
9.5	3.11
10.2	2.99
11.1	2.97
12.4	2.91
13.5	3.75
15.4	2.61
16.4	2.55
17.3	2.52
18.4	2.49
20.4	2.39
22.4	2.35
29.5	2.24
38.0	2.13
49.6	2.15
66.0	2.11

$\alpha_\infty = 2.11$

APPENDIX III

CALCULATION OF THE THERMODYNAMIC CONSTANTS FOR THE SOLVOLYSIS REACTIONS

Experimental activation energies were calculated using the Arrhenius equation shown below:

$$k = A \exp[- E_{exp}/RT] \qquad (1)$$

where k = the specific rate constant,

A = the frequency factor,

E_{exp} = the experimental activation energy,

R = the gas constant, and

T = the absolute temperature.

A plot of $\ln k$ versus $1/T$ gives a straight line whose slope is $-E_{exp}/R$. The activation energies in this thesis were calculated by the method of least squares using the data shown in Appendix IV.

Eyring (35) has shown that it is possible to calculate the heat of activation from the experimental activation by using the equation

$$E_{exp} = RT + \Delta H^{*} - p\Delta v^{*} \qquad (2)$$

where p = pressure, and

Δv^{*} = change in volume during reaction.

For reactions in solution $p\Delta v^{*}$ is approximately equal to zero.

Eyring (35) has derived the following equation for reactions in solution for calculating the entropy of activation from the rate constant and the experimental activation energy:

$$\underline{k} = e\ \underline{kT/h}\ \exp[+\Delta\underline{S}^{*}_{c}/\underline{R}]\ \exp[-\underline{E}_{exp}/\underline{RT}] \qquad (3)$$

where $\underline{k}$ = Boltzman's constant,

$\underline{h}$ = Planck's constant, and

$\Delta\underline{S}^{*}_{c}$ = the entropy of activation.

A sample calculation is shown below for the methanolysis of tetra-O-benzoyl-α-D-glucosyl bromide in methanol:DMF (12:88) at 305.1° Absolute.

$\underline{k}$ = 11.0×10^{-5} sec.$^{-1}$

$\underline{E}_{exp}$ = 17,280 cal./mole

Therefore, $\Delta\underline{H}$ = 17,900 cal./mole

$\underline{k}$ = 1.38×10^{-16} ergs/°K

$\underline{h}$ = 6.62×10^{-27} ergs-sec.

$\underline{T}$ = 305.1° Absolute

$\underline{R}$ = 1.987 cal./g. mole/°K

Therefore,

$$\exp[\Delta\underline{S}^{*}_{c}/\underline{R}] = [\frac{11.0 \times 10^{-5}}{305.1} \times \frac{6.62 \times 10^{-27}}{1.38 \times 10^{-16} \times 2.72} \times \exp(\frac{17,280}{305.1 \times 1.99})]$$

and $\Delta\underline{S}^{*}_{c}$ = 21.9 e.u. From the familiar equation

$$\Delta\underline{F}^{*} = \Delta\underline{H}^{*} - \underline{T}\Delta\underline{S}^{*}_{c}$$

$$\Delta\underline{F}^{*} = 24,400 \text{ cal./mole}$$

In applying the theory of absolute reaction rates to reactions in solution, three major assumptions are made which are described below:

1. The same approach is used as Eyring (35) uses in gas-phase systems with the modification that the partition functions of the reacting species and the activated complex should contain terms accounting for the environment. Due to the lack of knowledge of partition functions in the liquid phase, the less fundamental approach of activities is used. In this work an even less fundamental approach has been used in that it has been assumed that the solutions are ideal and that the activity coefficients are unity.
2. It is assumed that the time average collision frequency in solution is the same in the liquid and gas phases.
3. It is assumed that the transmission factor is approximately unity.

APPENDIX IV

DATA FOR CALCULATION OF ACTIVATION ENERGIES

TABLE XXVII

METHANOLYSIS OF TETRA-O-ACETYL-α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

$1/T \times 10^5$ deg.$^{-1}$	$k \times 10^5$ sec.$^{-1}$
301	11.40
308	4.71
318	1.55
322	1.12

Correlation coefficient = 0.998
Activation energy = 21,100 ± 1400 cal./mole

TABLE XXVIII

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

$1/T \times 10^5$ deg.$^{-1}$	$k \times 10^5$ sec.$^{-1}$
318.1	25.1
324.3	14.9
333.1	7.4

Correlation coefficient = 0.999
Activation energy = 16,400 ± 940 cal./mole

TABLE XXIX

METHANOLYSIS OF TETRA-O-BENZOYL-α-D-GLUCOSYL BROMIDE IN METHANOL:DIOXANE (9:1)

$1/T \times 10^5$ deg.$^{-1}$	$k \times 10^5$ sec.$^{-1}$
318.3	.47
324.3	1.24
333.1	3.01
343.4	5.19

Correlation coefficient = 0.999
Activation energy = 19,190 ± 895 cal./mole

TABLE XXX

METHANOLYSIS OF TETRA-O-BENZOYL-α-D GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

$1/T \times 10^5$ deg.$^{-1}$	$k \times 10^5$ sec.$^{-1}$
317.3	27.5
322.5	13.8
325.3	11.0
332.8	5.7
336.8	4.6
342.8	2.9
349.5	1.4

Correlation coefficient = 0.995
Activation energy = 17,280 ± 675 cal./mole

TABLE XXXI

METHANOLYSIS OF 2,3,6-TRI-O-BENZOYL-α-D-GLUCOSYL BROMIDE IN METHANOL:DMF (12:88)

$1/T \times 10^5$ deg.$^{-1}$	$k \times 10^5$ sec.$^{-1}$
307.5	175.3
313.2	103.0
318.3	77.3
321.5	60.4
327.7	50.1
332.7	20.4
342.8	11.4

Correlation coefficient = 0.986
Activation energy = 15,300 ± 575 cal./mole